Textbook of Clinical Pharmacology

As per the latest NMC Guidelines |
Competency Based Medical Education (CBME)
Curriculum under Graduate Medical Education Regulation

Rashmi Singla

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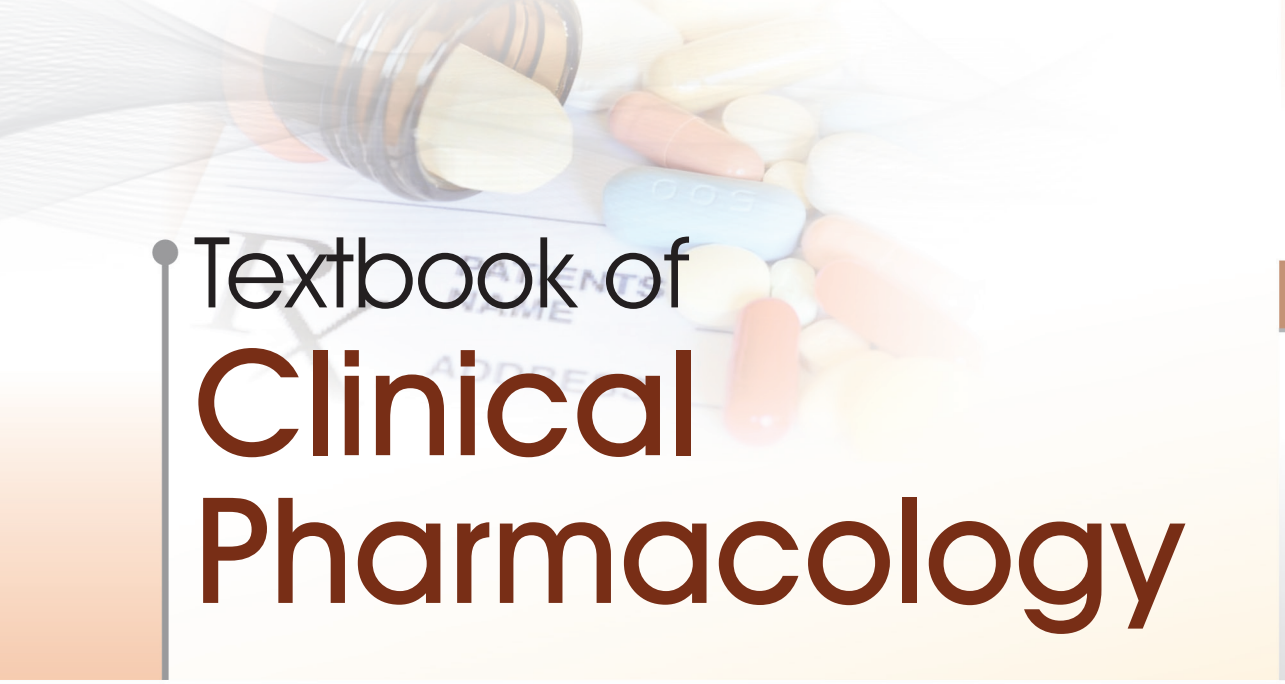

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to
my loving parents
with the blessings of Almighty

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Foreword

The changes in all fields of medicine are taking place at an explosive rate. This is particularly true for the branch of pharmacology where fast-paced research is adding on a plethora of knowledge. Each decade heralds new understanding of drugs and their uses in the face of newer challenges faced by our fellow clinicians. A notable development of modern medicine is the emergency of new clinical specialities and sub-specialties. The domin of practice in each of these fields calls for a different approach in deciphering the application of drugs.

Erstwhile literature in pharmacology has largely focused on its basic sciences' approach. This has often quizzed the clinicians and forced them to develop their own understanding and interpretation of drugs while largely relying on clinical experience and knowledge disseminated through annals of clinical literature. This has often created a gap in the tenets of pharmacology and its applied aspect as desired by the clinicians in different walks of medicine.

The present book is a good effort in harmonising the emerging scientific concepts of drug usage and the requirement of clinicians of diverse fields. The book aims at providing the latest background knowledge of each drug that the clinician of each speciality endeavours to use of his patients. The amalgamation of contributions from clinicians, faculty and research scientists of multiple fields has given a flavour to the book that each doctor can relish in his own space. To that end extend my congratulations to the principal author Dr Rashmi Singla and the Editor who have caught the imagination of present-day doctors, residents and teaching faculty alike.

I am confident that this textbook will find its utility space for the practitioners of multiple disciplines of medicine and also the students of undergraduate and postgraduate medicine in honing their clinical skills.

My best wishes to the team.

Prof (Dr) Hemchandra Pandey
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Preface

The subject pharmacology basically finds its application in clinical practice in the medicine field. Since pharmacokinetics and pharmacodynamics of the drugs are already discussed in various standard textbooks of pharmacology in detail, I felt the need to write a book *Textbook of Clinical Pharmacology* which could explain the pathophysiology, clinical signs and symptoms of the common diseases of each physiological system, investigations, treatment and any salient points about the drug in a simple lucid way and easy language. It gives narration as a story which unwinds itself smoothly and neatly. Also, any important adverse effects to be monitored or observed and any important drug interactions clinically are mentioned. The dosage and route of administration are clearly mentioned for the treatment. The relevant diagrams and tables are also provided where needed. The text begins with general pharmacology section covering drug dosing in different situations and subsequently it discusses the common diseases of each system, their clinical features, complications, prognosis and treatment, e.g. CVS pharmacology, CNS pharmacology, GIT, endocrine, psychiatric pharmacology, pharmacology for blood disorders, pharmacology in infectious diseases, etc. In the last section, it covers important chapters on dermatological pharmacology, ophthalmic pharmacology, pediatric pharmacology, drugs used in dentistry, emergency medicine and about treatment of dengue and COVID pandemics.

This book tries to enwrap almost all the clinical branches of a hospital to discuss in a nutshell all the aspects about the common medical ailments in IPD and OPD. The charm of this book is that it contains enriched contributions with clinical experience of specialists from different fields. The second-year and final-year students can read this book to get knowledge in their clinical postings and to do any case presentation. Also, it will help the intern students and beginning clinicians including PG residents to brush their knowledge by reading this concise book and apply their previous-read theoretical knowledge in the light of practical aspect of clinical pharmacology. And this will also save time to treat patients under one roof, without going through exhaustive theory textbooks of medicine, surgery, psychiatry, gynecology and obstetrics, ophthalmology, pediatrics, dermatology and dentistry.

I thank all the contributing authors from pediatrics, ophthalmics, medicine, pulmonology, gastroenterology, orthopedics, neurology, anesthesia, cardiology, plastic surgery, and dentistry, to give valuable inputs into the book. I thank Dr Ashutosh Sayana, our respected Principal and Dr Sanjay Gaur, my Head of the Department of Pharmacology, in encouraging me to complete this work. I also thank Dr Rizvi, Professor, Department of Ophthalmology, Government Doon Medical College, in guiding me to write a good book. I also thank Dr Harish Basera, Associate Professor, Department of Medicine, Government Doon Medical College, in giving his valuable inputs in the manuscript. I also adore arduous support of my loving parents and appreciation of my dear students in writing this book.

Rashmi Singla

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Chapter 1

Rational Drug Use in Clinical Practice

Drug therapy requires knowledge, judgement, skill and also sense of responsibility. The term 'rational drug use' means to prescribe drugs in appropriate dose for the appropriate period to the patient at an affordable cost. The aim is to promote better and more effective use of the drugs through consideration of efficacy, safety, convenience and cost. Recently, there has been irrational use of drugs due to number of reasons:

- There is lagging knowledge about continuing education and training in pharmacology.
- Drug regulatory authority is not well-organized and there is inappropriate supply of drugs.
- Availability of large number of drugs in the market.

Factors leading to sudden realization of rational drug use:

- New drugs have been discovered due to drug explosion.
- Drug resistance to be overcome is a challenge. There are continuing efforts to prevent development of resistance.
- Awareness about right drug use is increasing.
- Cost of treatment is an issue.
- Consumer Protection Act (CPA) sues the doctors against malpractice and negligence.

Important steps in rational drug prescribing:

- The patient's problem has to be defined.
- The therapeutic objective has to be specified.
- To choose treatment:
  1. Advice and information
  2. Treatment without drugs
  3. Treat with drugs
  4. Referral
  5. Combination of above

Start treatment and provide the patient with clear instructions and information. Monitor the treatment.

Defining the patient's problem: This is the first and most crucial step towards rational drug use. Patient makes a presenting complaint and right diagnosis is made by integrating many pieces of information like complaints of the patient, detailed history of episode, physical examination, lab investigations, etc.

Specify the therapeutic objective: Before starting the treatment, doctor should be clear what she/he wants to achieve. Having established the therapeutic objective, it will limit the treatment possibilities and will prevent lot of unnecessary drug use.

Following criteria for rational drug use should be met:

Efficacy: Efficacy is the first criterion for selection, e.g. in patients with congestive heart failure (CHF), loop diuretics are more efficacious than thiazide group of diuretics.

Safety: A rational drug use should be safe with no or minor side effects. Every drug has side effects. So, risk *versus* benefits have to be weighed. The risk is concerned with the properties of the drug, prescriber, patient, environment, e.g. benzodiazepines (BZPs) are safer than barbiturates or hypnotics for treating many conditions like anxiety, insomnia and seizures.

Convenience: It is another important factor for choosing P-drug. If this factor is not taken into account, patients may not be able to take the drug when needed, e.g. nitroglycerine (NTG) is available as tablets, as IV formulation. During the attack of angina, sublingual tablets of nitroglycerin (400 µg) are more convenient and so are P-drugs in that condition.

Cost: The prescriber's ideal choice is based on efficacy and safety, especially in the case of 'me too drugs'. The generic name should be prescribed as it is cheaper than the branded name while efficacy and safety in most of the cases are same.

Suitability: This applies to an individual patient. Before starting the treatment, it should be seen if the drug could be used in a particular patient because the patient may have certain conditions for which the P-drug may be contraindicated, e.g. β-blockers are contraindicated in bronchial asthma. To determine suitability, we need to know contraindications, alteration in pharmacodynamics/kinetics in presence of comorbidities, food drug interactions, dosage in elderly and children, etc.

A newly introduced drug is not always better and safer than the existing drug. Of the same drugs available, it is definitely more expensive. Moreover, the new drug's safety can be established after several years of use. So, choose a familiar drug whose effect is known. Choosing a patient with broad therapeutic umbrella (broad spectrum cephalosporins and chloramphenicol) is indicated in life-threatening situations for 2–3 days until a specific diagnosis is made.

Treatment with P-drugs: The market is flooded with drugs, which can be used to treat a particular condition. Reviewing all possible drugs for each and every patient can be a time consuming process. P-drug concept is used to solve the problem. P-drugs are familiar medicines prescribed regularly by doctors for a given condition.

Selection of P-drug involves the five basic steps:

1. Make the diagnosis.
2. The therapeutic objective should be targeted.
3. An inventory of effective groups of drugs should be prepared.
4. An effective group, is chosen according to criteria.
5. Out of the group, P-drug is selected.

Example: A man, 60-years old had presenting complaints of having several attacks of suffocating chest pain during exertional activity last month. The pain subsided on rest. He is non-smoker, has family history of heart attack. He is not on any medication in the past years, except occasional aspirin use. On auscultation, a murmur was found over the right carotid

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artery and the right femoral artery. Physical examination revealed no other abnormalities. Blood pressure is 130/85, pulse 78 regular, and body weight is normal.

Step I: Define the diagnosis. The patient is diagnosed as a case of stable angina pectoris due to coronary occlusion.

Step II: The therapeutic objective is targeted. The aim of treatment is to abate an attack as soon as it starts. The oxygen need of the cardiac muscle is reduced and workload on heart is decreased by decreasing the preload, the contractility, the heart rate or the afterload of the cardiac muscle.

Step III: An inventory of effective groups of drugs is prepared.

There are three groups with such an effect: Nitrates, beta-blockers and calcium channel blockers. Their sites of action are summarized in Table 1.1 and their comparison in Table 1.2.

Step IV: Nitrates is the chosen group (Table 1.3).

Table 1.1: Sites of action for drug groups used in angina pectoris

Groups	*Preload*	*Contractility*	*Frequency*	*Afterload*
Nitrates	++	–	–	++
Beta-blockers	+	++	++	++
Calcium channel blockers	+	++	++	++

Table 1.2: Comparison between the three drug groups used in angina pectoris

Efficacy	*Safety*	*Suitability*
1. **Nitrates** Pharmacodynamics Peripheral vasodilation Tolerance (especialy with constant blood levels) Pharmacokinetics High first pass metabolism Varying absorption in the alimentary tract (less in mononitrates) Glyceryl trinitrate is volatile: Tablets cannot be kept for long	*Side effect* Flushing, headache, temporary tachycardia Nitrate poisoning due to long-lasting oral dosage	*Contraindictions* Cardiac failure, hypotension, raised intracranial pressure Anaemia Fast effect dosage forms: Injection, sublingual tablet, oromucosal spray.
2. **Beta-blockers** Pharmacodynamics Reduced heart contractility Reduced heart frequency Bronchoconstriction, muscle vasoconstriction, inhibited glycogenolysis Pharmacokinetics Lipophilicity increases passage through blood–brain barrier	*Side effects* Hypotension, congestive heart failure Sinus bradycardia, AV block Provocation of asthma Cold hands and feet Hypoglycaemia Drowsiness, decreased reactions, nightmares	*Contraindications* Hypotension, congestive heart failure Bradycardia, AV block, sinus syndrome Astma Raynaud's disease Diabetes Liver dysfunction Fast effect dosage forms: Injection

Contd.

Table 1.2: Comparison between the three drug groups used in angina pectoris		
Efficacy	***Safety***	***Suitability***
3. **Calcium channel blockers** Pharmacodynamics Coronary vasodilatation Peripheral vasodilatation (afterload) Reduced heart contractility Reduced heart frequency	*Side effects* Tachycardia, dizziness, flushing, hypotension Congestive heart failure sinus bradycardia, AV block	*Contraindications* Hypotension Congestive heart failure, AV block, sick sinus syndrome Fast effect dosage form: Injection

Table 1.3: Comparison between drugs with the group of nitrates				
	Efficacy	***Safety***	***Suitability***	***Cost/100 (£)****
1. **Glyceryl trinitrate** Sublingual tab 0.4–1 mg cap 1–2.5 mg Transdermal patch 16–50	NB: Volatile 0.5–30 min 0.5–7 mg 1–24 hours 1–24 hours NB: Tolerance	No difference between individual nitrates	No difference between individual nitrates	0.29–0.59 3.25–4.28 42.00–77.00
2. **Isosorbide dinitrate** Sublingual tab 5 mg Oral tab 10–20 mg Oral tab (retard) 20–40 mg	2–30 min 0.5–4 hours 0.5–10 hours NB: Tolerance			0.45–1.51 1.10–2.15 9.52–18.95
3. **Pentaerythritol tetranitrate** Oral tab 30 mg	1–5 hours			4.45
4. **Isosorbide mononitrate** Oral tab 10–40 mg Oral tab/caps (retard)	0.5–4 hours 1–10 hours NB: Tolerance			5.70–13.30 25.00–40.82

*Indicative prices only, based on prices given in the British National Formulary of March 1994.

Step V: *Choose a P-drug*: In general, three drugs are available for the treatment of an acute attack: glyceryl trinitrate (nitroglycerin), isosorbide mononitrate and isosorbide dinitrate (Table 1.3). The first two drugs in table can be given sublingually with a rapid effect. Efficacy and safety of three drugs are the same. Concerning suitability, the three drugs hardly differ in contraindications and possible interactions. So ultimate criteria is cost. As can be seen from Table 1.3, costs may vary considerably. Since tablets are cheapest in most countries, these can be the first choice. In this case, P-drug of choice for an attack of angina pectoris would be: Sublingual tablets of glyceryl trinitrate 1 mg.

Fixed drug combinations are often used as they make drug therapy simple for convenience and better patient compliance. Synergistic combinations are, e.g. cotrimoxazole and trimethoprim, carbidopa + levodopa. Also, the side effects on one drug are mitigated by the other, e.g. a thiazide and a potassium sparing diuretic. Combined treatment is also given to prevent drug resistance, e.g. multidrug therapy (MDT) in tuberculosis (TB), HIV and falciparum malaria.

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CHOICE OF ANTIMICROBIAL THERAPY

Chemotherapy may not be required in certain indications like abscesses where surgical drainage is useful or in case of urinary obstruction. Broad spectrum antibiotics are given in case of unidentified pathogen and susceptibility. The parenteral route is used in case of emergency, e.g. septicemia or if the drug is not absorbed orally, e.g. gentamycin and vancomycin. After confirmation by culture and sensitivity test, narrow spectrum best antimicrobials are selected for treatment. The optimum dose and frequency must be administered. Inadequate doses cause microbial resistance. The therapy should be continued for sufficient time to prevent relapse after clinical cure, e.g. in typhoid fever, TB and infective endocarditis. Acute infections need 5–10 days treatment and prolonged therapy is avoided to prevent adverse drug reactions. In some diseases of urinary tract infection (UTI), culture report is required to show sterile sample as clinical symptoms disappear before eradication of the microorganism. When the risk of infection is high, e.g. at operative sites or when infection chances are low, but if happens can be disastrous, e.g. infection of heart valves, chemotherapy for surgical and dental procedures are given prophylactically. Some drugs need dose reduction or are contraindicated in hepatic and renal dysfunction or some genetic factors like G6PD deficiency. If a patient is already on treatment with some other drug, then the antimicrobial should be chosen avoiding any drug interactions, e.g. theophylline and erythromycin are not given together.

The misuse and irrational prescribing of antibiotics has led to emergence of resistance among antimicrobials and is a great concern nowadays. The infections with antibiotic resistant organisms have poorer prognosis. Resistance can be due to spontaneous mutation, transmission of genes from other organisms, production of enzymes that modify the drug, e.g. β-lactamases hydrolyse penicillins, efflux of drug from bacterial cell, e.g. meropenem resistance in *Pseudomonas aeruginosa*, modification of target site. Also, the antimicrobial use may lead to suppression of part of normal bacterial flora in patients which can cause multiplication of opportunistic pathogens, e.g. *Candida albicans*, *Clostridium difficile* pseudomembranous colitis caused by clindamycin. Moreover, broad spectrum antibiotics alter bacterial flora in the gut causing vitamin B complex and vitamin K deficiency as these are synthesized by intestinal bacterial flora.

Prescription writing: A prescription is the physicians' written order to the pharmacist for dispensing medication. It is a legal document for which the prescriber and the pharmacist are both responsible and subject to local regulations. It is prima facie evidence in the court of law. The salient feature of prescription is that it should be clearly state precisely what should be given. Few take words are still used but whenever possible, the language which the patient can easily understand should be used. The use of words like "take as directed" 'every 8 hourly', SOS is confusing and should be avoided and exact method and time should be mentioned. A prescription should include—name, address, age of the patient, doctor details, generic name of the drug, dosage form, total amount, label, instructions and warning, signature/initials of the prescriber (Fig. 1.1).

Superscription contains doctor and patient particulars and the symbol Rx in the name of the God of Remedies 'Jupiter'.

Inscription is the body of the prescription which contains name of the drug, dosage form and route of administration and the duration.

Patient's name: ..... Age: ..... Gender:	**SUPERSCRIPTION**	Doctor's name: ..... Qualification: ..... Reg no.: .....
Body weight: ..... Address and phone no. :		Address: ..... Contact details: .....
Diagnosis		
Rx		
Refills: Don't substitute/generic substitiution allowed	Inscription Subscription Transcription	DOC DOC stamp Sign and date

Fig. 1.1: Format of prescription

Subscription is the direction to the pharmacist regarding fulfilling the prescription.
Transcription is the instructions given to the patient by the physician.
Signature: The physician's handwritten signature will validate the prescription and allow the pharmacist to dispense the prescribed medicine.
Compliance: Long-term therapy to be successful requires patient and doctor compliance.
Patient compliance means how much the patient behaves according to the instructions given by the doctor. If the patient does not comply, it can lead to therapeutic failure in both routine practice and in scientific trial. Poor patient compliance may be due to:

1. Lack of faith in patient–doctor relationship—the doctor should inculcate trust in the patient so that he complies to his instructions. Patients should be made informed partners in treatment and encouraged to express themselves, i.e. patients should be told about the benefits and risks of treatment.
2. Unintentional non-compliance—is connecting drug intake with tasks in daily life (breakfast, bedtime) or by using calendar path.
3. Intelligent non-compliance is when a patient willfully decides not to take the drug. Reasons may be:
   - Due to side effects
   - Improvement in patient's mental condition
4. Lack of information: Most of the patients have been found unable to recollect verbal instructions. Nowadays, patient-friendly information cards are given by the doctor, pharmacists and a package insert by pharmaceutical companies.
5. Frequency and complexity of drug regimens: Patient compliance is inhibited by polypharmacy; more than 3 drugs are given.
6. Anxiety-on being newly diagnosed suffering from a disease, doctor may explain the drugs and how to take but the patient's thoughts are drifting away. The patient is often worrying about new illness and its consequences.
7. Inappropriate health benefits
8. Poverty
9. Psychiatric conditions

All these factors must be considered and modified to enhance patient's compliance.
Overcompliance: Taking more drugs than prescribed leads to overcompliance.

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Doctor's compliance is the professional conduct of doctors on their part:

- They should use only drugs about which they are well-informed.
- Sufficiently approved new advances are to adopted only.
- To prescribe accurately.
- To refrain from inappropriate prescribing.
- To tell what the patients need to know.

The doctor should explain to the patient the effects of the drug, side effects, instructions about how, when the drug should be taken, warning about the drug, future consultation when to come for follow-up or earlier.

Monitor the Treatment

Was the treatment useful—Yes/No?
If disease cured, stop treatment.
No, if the disease is not cured, any side effects, yes, reconsider dosage or drug choice.

Irrational drug combinations: The national list of essential medicines published in 2022 contains 384 medicines and 23 fixed dose combinations, whereas in India, there are innumerable examples of irrational drug combinations, which are easily available and can be bought without necessarily giving a prescription.

Following needs to be done to prevent irrational prescribing:

- A rational and logical basis for bringing out a fixed dose formulation should be done.
- The misleading claims by the medical representatives and pharmaceutical industry should be taken care of.
- The practitioners should acquire the necessary knowledge and skills to prescribe rationally.
- There should be mandatory adverse drug reaction (ADR) reporting as in developed countries.
- Drugs and therapeutic review committees should be constituted in hospitals to rationalize prescribing.
- Trainings should be held for students and doctors in medical colleges to assess new drug combinations more logically.

SOURCES OF DRUG INFORMATION

To keep updated with drugs: With new drug development, a physician should know about advancements in drug therapy.

Due to lack of well-organized system for giving the latest information to physicians, pharmaceutical companies have exploited the scene. Information from pharmaceutical companies is readily available through a number of media. Medical representatives advertise at professional meetings, put advertisement in journals, or by mailing. They highlight the positive aspects of products for promotion and overlook or give little coverage to negative aspects. For analyzing the available aspects, following rules should be followed:

- More information should be acquired than from the advertisement.
- Look for authenticity of references.
- Only quality references should be taken seriously.

All the sources of the latest drug information available are:

Reference books: A reference book should be chosen based on the frequency of new editions. Reviews of books every 2–5 years can provide updated knowledge, e.g.

- Goodman and Gilman's: The Pharmacological Basis of Therapeutics
- Martindale the Extra-pharmacopoeia
- Monthly Index of Medical Specialities (commercially sponsored drugs using complete and comparative assessments.)

National list of essential drugs and standard treatment guidelines: It is a list of essential drugs chosen for each level of care of dispensary—the center, district hospital, referral hospital. Essential drugs are those that satisfy the basic healthcare needs of majority of the population. They should be available at all times in adequate amounts and in appropriate dosages.

The main priority of developing countries is the basic health care costs. The drugs occupy 40% of the healthcare budget leading to lack of funds available for other health services. The scheme of basic or essential drugs was suggested by WHO in 1945, to extend the accessibility of most necessary drugs. With advice of experts in public health, medicine, pharmacology, and pharmacy and drug management, a list of necessary drugs should be prepared up locally and periodically revised. India prepared its National Essential Drug List in 1996 that included a total of 279 drugs. Standard treatment guidelines document the preferred treatment for common health problems to promote therapeutic, effective and economically efficient prescribing.

Drug formularies and pharmacopoeias: Some information about the drugs' chemical and physical properties, methods of purification and identification and storage cannot be obtained by textbooks, reviews or journals. Such information is provided by pharmacopoeias and formulary besides clinical indications, side effects, administration and dosage recommendations. Pharmacopeia provides information of drug substances and dosage forms by a committee of physicians, e.g. British Pharmacopeia, Indian Pharmacopeia, European Pharmacopoeia. Formulary provides information about the pharmaceutical ingredients by the pharmacists committee, e.g. Pharmaceutical Codex, National Formulary of India. Pharmacopeia and drug formulary are collectively known as drug compendia, e.g. Physician's Desk Reference is published annually with supplements twice a year.

Drug bulletins are periodicals published weekly to quarterly.

Medical journals: Such as the Lancet, National England Journal of Medicine (NEJM), British Medical Journal (BMJ). They contain much information of relevance to prescribers. Good medical journals are peer reviewed, i.e. read by indigenous experts for their opinion prior to publications. Some journals are sponsored. They offer an easily digested format. They are physician's way to save time as they are reliable.

Verbal information is by consulting with specialists and gaining their practical experience or in more structured way through postgraduate (PG) training courses.

Drug information centers: Uppsala Monitoring Centre located in Uppsala, Sweden, is the World Health Organization Collaborating Center for monitoring of international drugs. It collects, assesses and communicates information from member countries, national pharmacovigilance centers in regard to the benefits, harms, effectiveness and risk of drugs. Health workers and sometimes the general public can call and get help regarding drug use, intoxication, etc.

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Electronic databases: Many major reference journals such as Martindale or Meyers side effects of drugs are now directly accessible through international electronic networks. Micromedex is an extensive subscription website maintained by Truven corporation. It provides for personal digital assistant devices, online drug dosage and interaction information, and toxicological information. Databases for drug and chemical information are Medline, National Library of Medicine, PubMed and Cochrane.

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Chapter
2

Clinical Pharmacokinetics

The knowledge of basic pharmacokinetic concept is essential for safe and appropriate use of drugs in the clinical setting. The pharmacokinetics of a drug can be described using few pharmacokinetic parameters—absorption, volume of distribution, metabolism and elimination of a drug.

1. Absorption

Bioavailability (BA) of a drug is the rate and extent to which it reaches the systemic circulation as intact drug after administration by any route. When the drug is administered by intravenous (IV) route, BA is naturally 100%. After administration by any route, the BA depends upon the fraction of drug clearance in the liver, besides pharmaceutical factors. It can be calculated as:

Oral BA = Fraction absorbed × 1-(ER)

ER = Extraction ratio

Removal of a drug by an organ can be specified as the extraction ratio, i.e. the fraction or percentage of the drug removed from the perfusing blood during its passage through the organ.

$$\text{Hepatic clearance} = \left[\frac{FuCL_{int}}{Q + FuCL_{int}}\right] \times Q$$

where, Q—hepatic blood flow: Fu—unbound fraction of drug; CL_{int}—intrinsic hepatic clearance—it is clearance of drug from plasma devoid of influence of blood flow or protein binding

$$\text{Extraction ratio} = CL/Q$$

Extraction ratio can be classified as high (>0.7), intermediate (0.3–0.7) or low (0.3). The extraction ratio is important in predicting which factors such as intrinsic factor, protein binding, blood flow, will alter the pharmacokinetic parameters of the drug. Drugs that have high extraction ratio have a large first pass effect and the bioavailability of these drugs after oral administration is low.

Clinical significance of BA Bioavailability has vital role in the absorption of any drug and its response. Its parameter will be helpful in proper and rational use of any medicine. There are number of factors which might affect the response of a drug due to changes in bioavailability of that particular medicine.

i. Route of administration, e.g. if BA after oral administration is low, the drug cannot be given by oral route, it has to be given parenterally, e.g. lidocaine, nitroglycerine.

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ii. Variability in drug response: There is greater inter-individual variability in drug concentration and response because small difference in first pass metabolism leads to large changes in BA.
iii. Relationship between oral and intravenous dose: This is determined by BA, e.g. if oral BA is 20%, then 5 times of IV dose has to be given orally to get similar plasma levels, e.g. propranolol.
iv. *Onset of action:* The time required to obtain peak plasma concentration and onset of action depends upon its rate of BA. It becomes vital when we need to select drugs with fast bioavailability in emergency condition where quick response of drug is desirable, e.g. antibiotics IV.

2. Distribution

Once drug enters the systemic circulation, the next process under pharmacokinetics is the distribution of drug to target site. So, distribution is second fundamental parameter in discussing drug disposition. Body fluid of human being is distributed into 3 main compartments—plasma, interstitial fluid and intracellular fluid (ICF). Drugs get distributed into these fluid compartments to varying extents. Extent of distribution can be determined with known amount of drug in the body.

Volume of distribution (VD): Once a drug gets access to the bloodstream, it gets distributed to other tissues depending on lipid solubility, ionization at physiological pH, extent of binding to plasma and tissue proteins, presence of tissue specific transporters (in brain and choroidal vessels), liver, kidney, GIT and differences in regional blood flow. Plasma protein binding property of drug has very important role in distribution of any drug inside the body. Interactions involving drug distribution are primarily due to displacement of one drug from its binding site on plasma proteins by another drug. Drugs highly bound to plasma proteins have a relatively small VD like oral anticoagulants, sulfonylureas. Certain nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptics are liable to displacement interactions.

Volume of distribution can be calculated as amount of drug in body/concentration in plasma.

If VD is 10–20 liters, e.g. aspirin, it indicates that a drug distributes out of plasma into the extracellular fluid (ECF), but does not enter the cells, e.g. hydrophilic drug with small molecular weight.

If VD is 22–40 liters (e.g. methyldopa), it implies that the drug reaches the ECF, but also manages to enter at least some cells, e.g. a lipophilic drug with small molecular weight.

VD > 40 liters indicates avid binding to tissues resulting in very small plasma concentration of the drug, e.g. chloroquine, digitoxin and imipramine.

Pathological states, e.g. congestive heart failure, uremia, cirrhosis of liver can alter the VD of many drugs by altering distribution of body water, permeability of membranes, binding proteins or accumulation of metabolites that displace the drug from the binding sites.

On the other hand, drugs such as digoxin, will not have much change in VD due to ascites since it itself has very large volume of distribution.

It has VD 6 L/kg because drugs sequestrated in other tissues may have VD much more than total body water or even body mass. Digoxin is concentrated in the heart, skeletal muscle, liver and kidney.

In patients with chronic liver disease and hypoalbuminemia and ascites, plasma protein binding is decreased and VD is increased.

Clinical significance of VD

1. In designing dosage regimen

- **Loading dose:** If it is desired to reach a target plasma concentration quickly after initial dose or if quick repeated doses given in the beginning, it is called loading dose.

  IV Loading dose = VD × Target concentration

  We are giving a dose sufficient to provide the desired concentration in plasma when distributed throughout the volume available to it.

  The speed at which the loading dose is given depends on the therapeutic index of the drug. For a drug with narrow therapeutic index, the loading dose is given slowly, e.g. over 30 min for theophylline and over 24 hours for digoxin. It may be given IV/orally depending upon the urgency of action. When given orally, bioavailability of drug has to be taken into account.

  Oral loading dose = VD × Target plasma concentration/BA

  where, BA—bioavailability.

2. It helps in estimating the total amount of drug at certain time in body.

Amount of drug = VD × Plasma concentration of drug at certain time

3. Hemodialysis: Another clinical application of VD is predicting usefulness of hemodialysis in cases of drug toxicity due to overdose. A small VD implies that most of the drug present in body is in plasma or blood. In overdose with such a drug, hemodialysis will be useful for quickly eliminating drug present in the body, e.g. aspirin overdose and methanol poisoning. This would not be made true if a drug is extensively bound to plasma proteins, since bound drug will not be filtered by hemodialysis, e.g. teicoplanin and ceftriaxone.

3. Biotransformation (Metabolism)

Once drug has acted upon its target after distribution, this drug needs to be eliminated from the body so that toxicity could be avoided. So, now human body will do the chemical alteration of the drug to render non-polar compounds polar to be excreted easily as they are not reabsorbed in the renal tubules. The drugs can be metabolized in the liver, kidney, intestines, lungs and plasma.

There are two types of reactions by which any drug can be metabolised in our body, i.e.

1. The non-synthetic phase I reactions are oxidation, reduction and hydrolysis–where a functional group is added or removed rendering the metabolite active or inactive.
2. The synthetic phase II reactions are conjugations—glucuronide, sulfate, glutathione, glycine conjugations, acetylation, methylation and ribonucleoside synthesis. The microsomal and non-microsomal enzymes catalyse these reactions. The microsomal enzymes are present in the liver, kidney, intestinal mucosa and lungs and catalyse phase 1 reactions and glucuronidation. The non-microsomal enzymes are present in the cytoplasm and mitochondria of hepatic cells and in other tissues including plasma. They catalyse some oxidations, reductions and all conjugations except glucuronidation.

The consequences of microsomal enzyme induction are: Inactivation of drugs by metabolism, e.g. oral contraceptives (OCPs), toxicity of drugs that are activated by metabolism, e.g. paracetamol, intermittent use of an inducer may interfere with adjustment of dose of another drug, e.g. oral anticoagulants, hypoglycemics, antihypertensives and antiepileptics.

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Inhibition of drug metabolism is clinically significant if drugs utilize the same enzyme, e.g. ritonavir is CYP3A4 inhibitor and lowers the dose of other protease inhibitors given concurrently because they are metabolized by CYP3A4 isoenzyme.

Various pathophysiological mechanisms that may lead to altered disposition of the drugs due to liver disease:

- Decrease in absolute cell mass
- Alterations in hepatic blood flow
- Impaired biliary elimination
- Enterohepatic cycling may be altered leading to increase or decrease in bioavailability.
- Altered volume of distribution.
- Hepatorenal syndromes—which refers to renal impairment linked solely to liver impairment.
- Changes in plasma protein binding with indirect effects on drug clearance.
- Hepatic clearance—there are three groups of drug clearance:

A. Flow-dependent drugs: Hepatic blood flow rate is perhaps the sole criterion on which the hepatic clearance depends for the highly extracted drugs (with extraction ratio (E >0.7). The drugs with high extraction ratio undergo significant first pass elimination by the liver following oral administration. There is impairment of hepatic clearance when liver blood flow is reduced as in heart failure, in severe cirrhosis and other forms of liver failure. A small decrease in the hepatic extraction ratio may lead to a subsequent increase in bioavailability, e.g. propranolol, pethidine, pentazocine, labetalol, morphine, verapamil, etc.

B. Capacity-limited drugs: The disposition of poorly-extracted or capacity-limited drugs is more sensitive to changes in plasma protein binding and or free intrinsic clearance than to alterations in hepatic blood flow.

i. *Capacity-limited-binding-sensitive drugs:* These are the drugs which are highly bound to plasma proteins (fraction unbound <0.155). Their hepatic clearance depends on the extent of plasma binding as well as free hepatic intrinsic clearance. Patients with hepatic disease may have a low serum albumin secondary to accumulation of fluid or decreased production.

   A decrease in plasma protein binding increases hepatic clearance, resulting in decreased total drug concentration, but free drug concentration does not change if free intrinsic clearance remains unchanged, e.g. phenytoin, valproic acid, quinidine, warfarin, salicyclic acid, etc.

ii. *Capacity-limited-binding-insensitive drugs:* These are the drugs which are minimally bound to plasma proteins. In this case, hepatic clearance depends only on the free intrinsic clearance of the drug, e.g. diazepam, nitrazepam, phenobarbitone, carbamazepine, naproxen, etc.

C. Intermediate extraction ratio drugs: For drugs with intermediate extraction ratio values (0.3 < E <0.7), hepatic clearance may be altered due to alterations in hepatic blood flow, plasma protein binding and free intrinsic clearance, e.g. aspirin, codeine, quinidine

Child-Pugh score is a scoring system to measure the severity of chronic liver disease in patients with cirrhosis. It identifies patients as class A, B or C based on albumin, bilirubin concentration (S), prothrombin time, presence of ascites or encephalopathy.

Class A: (5–6 points)—well compensated liver disease—favourable prognosis

Class B: (7–9 points)—moderately advanced liver disease

Class C: (10–15 points)—decompensated cirrhosis requires liver transplantation

Drug-metabolizing capacity of liver depends on several different enzyme systems which may be compromised to a varying degree by hepatic disease, thus producing considerable interpatient variability in pharmacokinetic parameters, e.g. for diazepam, nitrazepam, carbamazepine, phenobarbital, indomethacin and caffeine.

Elimination Half-life

Half-life of elimination is the time taken for the amount of drug in the plasma concentration to fall by ½. It is determined by CL and VD.

$$\text{Half-life} = 0.693 \times \text{VD}/\text{CL}$$

Therefore, it is a secondary parameter and it is increased by increase in VD and decline in CL and *vice versa*. In disease states, e.g. renal and hepatic failure, CL and VD can change.

Clinical Significance of Half-life

- **Time for plasma concentration to fall after stopping drug:** Since half-life gives the rate of elimination at which plasma concentration of a drug decreases once dosing is stopped. After 4–5 half-lives, most of the drug is eliminated and concentration falls to negligible levels. This knowledge is particularly important in drug toxicities where measures to remove toxic drug from the body will only be useful if undertaken within 5 half-lives.
- **Time to reach steady state with chronic dosing:** When multiple doses or continuous infusion of a drug is given, the plasma concentration rises till a state is reached where rate of administration is equal to rate of elimination, is called steady state. When dosing is stopped in 4–5 half-lives, the drug reaches 94–97% of the steady state concentration. This is also true for intermittent bolus dosing, where though the plasma concentration will fluctuate during each dosing interval, average plasma concentration will remain more or less constant once steady state is reached. Understanding steady state is importent for choosing right dose and dose interval to reach a steady state concentration.
- **Loading dose:** If half-life of any drug is long, it will take a long time to reach desired plasma concentration. So, with such drug having long half-life of drug, we need higher dose to achieve steady state concentration.
- **Duration of action and dosing:** If daily dose is constant and the frequency of administration is increased, though the steady state will remain same, but there will be fluctuation in plasma concentration with peak (toxicity) and trough (loss of therapeutic effect). This is important for drugs with low therapeutic index such as digoxin or aminoglycosides. If dose rate is changed, a new average steady state concentration (CPSS) is attained over the next 4–5 half-lives.
- **Dosing frequency required to avoid too large fluctuations in plasma concentration during the dosing interval:** With multiple dosing, the extent of fluctuation is determined by half-life, dosing interval and absorption rate. If absorption is immediate and complete, fluctuation depends solely on dosing interval in relation to half-life. If a drug is given every half-life, then over one half-life, the concentration falls to half the peak concentration, i.e. the

peak concentration will double the trough concentration and the fluctuation will be 1.005. If the drug is given less frequently, then its half-life fluctuation will be small and *vice versa.*

4. Clearance

It is defined as the volume of blood cleared of drug per unit time. It describes the efficiency of irreversible elimination of a drug from the body. Elimination includes, both excretion in urine, faeces, air, etc. and metabolism into different compounds. Clearance by different organs is additive, i.e.

Clearance total = CL (renal) + CL (hepatic) + Others.

For most drugs, CL is constant over plasma concentration range used in clinical settings, i.e. elimination is not saturable and rate of elimination is directly proportional to plasma concentration, i.e. a constant fraction of drug is eliminated per unit time, e.g. phenytoin. Such drugs are said to undergo first order kinetics or linear kinetics. For drugs with zero order kinetics or non-linear kinetics, a constant amount of drug is eliminated per unit time irrespective of plasma concentration, e.g. ethyl alcohol. The elimination of some drugs approaches saturation over the therapeutic range and change over from 1st order to zero order kinetics. The plasma concentration increases disproportionately with increase in dose, e.g. phenytoin, warfarin.

Renal CL: It is the rate of excretion of drug related to its concentration in blood or plasma.

$$CL\ renal = U \times VD.$$

U = concentration of drug in urine/concentration of drug in plasma

VD = volume of distribution

Renal CL is the net result of three different processes:

1. Glomerular filtration
2. Active tubular secretion.
3. Passive tubular reabsorption.

Renal CL = Filtration + Secretion–Reabsorption.

Since only free or unbound drug can be filtered at glomerulus and filtration depends on (GFR).

$$CL_R = [(F_u \times GFR) + [Q \times F_u \times C/[Q + (F_u \times CL_i)]/[Q + (F_u \times CL_i)]] \times (1-F_r)$$

F_u = unbound fraction of the drug, CL_R renal clearance, Q is renal blood flow, CL_i is intrinsic renal CL. F_r is fraction of the drug reabsorbed from the tubule lumen.

Equation gives a fair index about the relative importance of tubular secretion and reabsorption in renal excretion of a drug. If total renal CL is >GFR, this means the drug is most likely being cleared by active secretion, if renal CL is <GFR, some of it is reabsorbed in the tubules. If Renal CL = GFR, it is neither secreted nor reabsorbed.

Clinical Significance of Clearance

CL determines the maintenance dose rate of a drug. To keep the concentration of a drug at a particular steady state concentration, it should be understanding effects of physiological and pathological variables on drug elimination, e.g. in hepatic or renal disorder.

IV maintenance dose rate = $C_{ss} \times CL$ (L/hour).

C_{ss} = steady state concentration of drug in plasma

For oral route, bioavailability of drug has to be taken into consideration.

Oral maintenance dose rate = $C_{ss} \times CL/BA$

Renal disease or reduced cardiac output often reduces the clearance of drugs that depends on renal elimination. The most important renal variable in drug elimination is glomerular filtration rate and creatinine clearance is an indicator of GFR.

Dosage in patient with renal impairment = Average dosage for a normal person × patient's CL_a (patient's altered creatinine clearance/100 ml/min).

If a drug is 50% cleared by the kidney and 50% by liver and the normal dosage is 299 mg/d, the hepatic and renal elimination rates are each 100 mg/d at steady state. The corrected dosage in a patient with a creatinine clearance of 20 ml/min will be:

Dosage = 100 mg/d (liver) + 100 mg/d × 20 ml/min/100 ml/min

= 100 mg/d + 20 = 120 mg/d

If the serum creatinine clearance is S_{cr}, the altered clearance for the patient can be calculated as

$$CL_a = (140 - \text{Age}) \times \text{Body weight (kg)}/72 \times S_{cr}$$

A cause of renal failure is more likely to suffer from various non-renal ailments, like hypertension, congestive cardiac failure, nephropathy, bone disease, infection, anemia, etc. It is also likely to be subjected to different medications for various ailments. Furthermore, it is likely to respond in a different manner to these pharmacological agents. This different response may be due to abnormalities in urinary excretion, metabolism and sensitivity to drugs. In recent years, a number of nomograms have been published taking into account creatinine clearance, body weight and age of the patient, especially for drugs with a narrow therapeutic range such as gentamycin, kanamycin and digoxin. Prescribing for patients with renal disease requires knowledge of the drug biotransformation, dynamic profile, and duration of action and mode of excretion.

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Chapter
3

Posology (Dose Calculations)

It is the branch of pharmacology which deals with making calculations regarding the drug dosage.

1 ml = 15 drops (macrodrip set), 1 ml = 60 drops (microdrip set).

Dose in mg/ml = Rate (ml/min) × Concentration (mg/ml).

Problem 1: It is required to administer IV 2 mg of a drug. You have 5 ml vial containing 10 mg of the drug. How many ml are you going to draw up in a syringe?

Sol. The vial contains 10 mg in 5 ml = 2 mg /ml. So to give 2 mg, 1 ml is to be drawn in syringe.

Problem 2: Calculate concentration of drug of whose 1 g has been added to 250 ml of bag of normal saline.

Sol. Concentration = Amount of solute/Volume of solvent = 1000/250 = 4 mg/ml.

Problem 3: How many drops/min are required to infuse 1000 ml of normal saline over 24 hours using a microdrip set?

Sol. Drops/min = Volume to be infused × Drip set rate (drops/ml)/Infusion time in minutes
= 1000 × 15/2 × 60 = 125 drops/min

Problem 4: For a drug B, available in concentration of 2 g/500 ml, you are instructed by a senior consultant to administer it to a patient in dose of 3 mg/min. What rule will you set in a microdrip set?

Sol. Rate = Dose to be administered/Concentration of drug solution
= 3 × 500 × 60/2000 = 45 drops/min

Problem 5: During your bedside round, you notice that a drug is available in concentration of 1 g/500 ml, is being infused at rate of 20 ml/hr. What is the dose administered to the patient?

Sol. Dose = Rate × Concentration = 20 ml/hr × 1g/500 ml = 20 × 1000/500 = 40 mg/hr

Problem 6: A senior consultant orders to start a drug E at the rate of 10 µg/kg/min. Drug W is available as 1000 mg/500 ml. If the patient weighs 50 kg, at which rate will you infuse E in a microdrip set?

Sol. Rate = Dose to be administered/Concentration of drug solution
Drop rate = 10 × 50 × 500 × 60/1000 × 1000 = 15 drops/min

Problem 7: Your patient is receiving a drug D available as 800 mg/250 ml at a rate of 12 ml/hr. The patient weighs 40 kg. Calculate the dose in µg /kg/time.

Sol. Dose = Rate × concentration = 12 × 800 × 1000/60 × 250 × 40 = 9.14 µg/kg/min

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Chapter
4

Chronotherapeutics

All living organisms have rythms with varying frequency ranging from seconds to seasons. This rhythmicity helps all living systems survive by enabling them to adapt to the changing conditions. The circadian rhythm is the best-known chronological frequency, which approximates the earth's 24-hr rotation around the sun. Also, both disease states and drug therapy are affected by a multitude of rhythmic changes within the human body. This principle of varying circadian rhythm has been applied in the treatment of various disease states and is called chronotherapeutics. The field of chronotherapeutics is based on the delivery of medicines so that various amounts of drugs are delivered at different times in accordance with natural biorythms during a 24-hr period. Chronotherapeutics refers to:

- Drugs are given according to a person's daily, monthly, seasonal or yearly biological clock in order to optimize health benefits and minimize the adverse effects.
- Altering the biological clock: A sleep disorder can be treated by altering an individual's sleeping and waking times.

CHRONOTHERAPEUTICS

Chronotherapy is based on an interdependent relationship between the peak-to-trough rhythmic activity in symptoms of the disease and the risk factors, pharmacological sensitivity and pharmacokinetics of many drugs. The specific time, the patients take in their medication becomes more significant throughout the study so as to maintain constant drug levels throughout a 24-hour period.

There are some physiological processes which vary in circadian rhythm, e.g. morning rise in blood pressure and heart rate, decline in mid-afternoon and are minimum at midnight, gastric emptying time—rapid in morning. Many hormones like cortisol, cathecolamines, plasma rennin, aldosterone, and angiotensin are secreted in the morning. In contrast gastric acid, growth hormone, prolactin, melatonin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone peak in the evening or during sleep.

There are many diseases which show a circadian pattern. Some of the conditions benefited are—allergic rhinitis, inflammation, neoplastic—various forms of cancers, asthma, CVS disease [hypertension, angina, myocardial infarction (MI)] and peptic ulcer disease. The administration of drugs is done according to the circadian rhythm of the disease.

Table 4.1: Circadian rhythm of some diseases	
Disease	***Circadian rhythm***
Allergic rhinitis	Symptoms worse in morning
Bronchial asthma	Exacerbations most common during sleep
Osteoarthritis	Symptoms worse in middle/later part of day
Rheumatoid arthritis	Symptoms worse on awakenings
Angina, MI	Incidence higher in the morning
Stroke	Incidence higher in the morning
Peptic ulcer	Incidence higher in early morning

- **Allergic rhinitis:** Such patients suffer their worst symptoms when they wake-up in the morning. Administering an antihistamine at night provides better results in controlling this morning discomfort than the morning dose. If the drug has the peak pharmacological activity at the time of greatest distress, optimum relief may be provided to the patient.
- **Rheumatoid arthritis:** A non-steroidal anti-inflammatory drug (NSAID) such as ibuprofen effectively relieves pain if the drug is administered at least 4–6 hours before the pain reaches its peak intensity. So, NSAIDs are recommended before bedtime if patient experiences a particular high level of discomfort in the morning. Treatment with indomethacin once a day treatment scheme is more effective in controlling morning symptoms.
- **Asthma:** Asthma symptoms generally worsen at night and occur more at night than during the day. Hence, antiallergics and steroids are administered in the evening.
- **Heartburn:** The heartburn cases are worse after meals and at night. Acid secretion is greater between 10 pm and 2 am. The time of dosing of H2-blockers (antihistaminics) and proton pump inhibitors (PPIs) will determine their effectiveness. In a study conducted on a group of 18 healthy volunteers, 3 dosage regimens of omeprazole and ranitidine (Fig. 4.1) are equally effective. Patient compliance was better in single ingestion in the evening.
- **Peptic ulcer:** As the maximal acid secretion, pain and perforation of gastric and duodenal ulcers are more common at night, administration of these drugs at bedtime is more

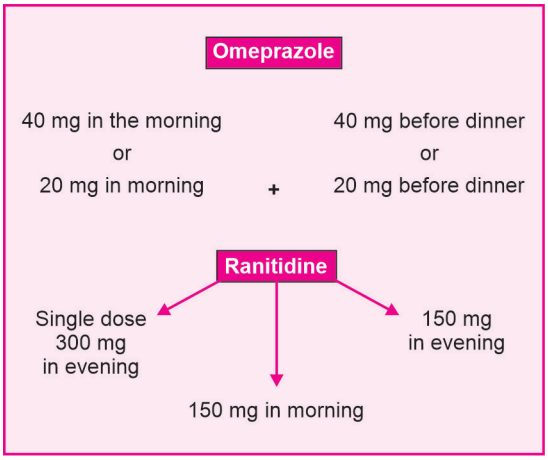

Fig. 4.1: Dose regimens in heartburn

effective. This not only decreases acid secretion more effectively but also promotes healing of ulcers and decreases their occurrence.

Hypertension: Cardiovascular (CVS) events including MI, stroke, and sudden death are more in the early morning hours, e.g. verapamil when administered at bed time, it provides optimal drug concentration between 4 am and noon. Also, propranolol and diltiazem are used as antihypertensives in chronotherapeutics.

Hypercholesterolemia: Clinical studies have shown that administration of Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors at nighttime lower serum cholesterol levels more effectively than the same dose given in the morning as HMG-CoA reductase enzyme activity is high during the night.

SKIN DISORDERS

Psoriasis: It is a chronic inflammation disease producing bumpy, flaky condition of skin due to high cell turnover which shows marked circadian variation. Inflammatory act highest at night:

- In epidermis—highest cell turnover is between 9 pm and 3 pm.
- In dermis—highest at 9 pm.

Atopic dermatitis: Treatment depends on the circadian rhythm and skin sensitivity (itching) which is highest at night.

Skin cancer: Tumor regression is greater when DNA material of skin cells is replicating. With lidocaine the pain-relieving effect is of longest duration when injected at 15:00 hrs. Nicotine penetrates skin faster at 4 am. Topical corticosteroids activity is greater when applied in the afternoon.

Use of oral contraceptives to inhibit ovulation is the application of chronobiological principles.

Chronotherapeutics is a promising but still relatively new field. It is important that physician must understand the advantage which is best-traditional treatment or chronotherapy.

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Chapter
5

Dosing in Pediatric Group

As physiological processes mature significantly in the first year of life influencing pharmacokinetic variables—absorption, distribution, metabolism, excretion. The pharmacokinetics in infants should be paid attention to while drug dosing.

Drug absorption: The factors influencing the absorption of drug are blood flow to administration site, GIT function (gastric acidity and gastric emptying time).

A. GIT absorption: In full-term infants, the gastric acid secretion begins soon after birth and increases gradually over several hours in full term infants.

The emptying of gastric contents is prolonged in the first day or so after delivery. In premature infants, the gastric emptying time is slow leading to efficient absorption in premature infants. Peristalsis in neonates is irregular and may be slow. The enzyme activity of GIT is lower in the newborn than in adults. In infants up to 4 months of age, α-amylase and other pancreatic enzymes activity in the duodenum is low. Also, in neonates there is low concentration of bile acids and lipase leading to decreased absorption of lipid soluble drugs.

B. Other routes: An appropriate formulation is used for absorption by rectal route, e.g. diazepam, theophylline are used in uncooperative infant. Digoxin or gentamycin administered by intramuscular and subcutaneous routes give variable plasma concentrations, because of low proportion of skeletal muscle and fat in children. Absorption after injection is also guided by the rate at which blood flows to the muscle or subcutaneous area injected. Hazardous drugs are cardiac glycosides, aminoglycosides and anticonvulsants, if perfusion to the muscle suddenly increases resulting in increase in drugs entering the circulation causing toxicity. Due to incomplete development of blood–brain barrier (BBB) in newborn, certain lipid-soluble drugs, such as general anesthetics, sedatives, narcotic analgesics result in increased permeability. This is the reason for neonates and infants to be sensitive to these drugs. Drugs are given by intravenous route preferably in the seriously ill newborn. Topical applied drugs applied are readily absorbed due to well hydrated skin and thin stratum corneum.

C. Drug distribution: The neonate has a higher percentage of its body weight in the form of water (70–75%) than does the adult (50–60%). Hence, the volume of distribution increases for water-soluble drugs and so loading doses are required for some drugs, e.g. aminoglycosides.

Total body fat in preterm infants (born before 37th week of gestation), is about 1% of total body weight compared with 15% in full term infants. Another factor determining drug distribution is drug binding to plasma proteins. Neonates have low protein binding capacity.

Hence, fraction of free drug increases in plasma and for some drugs—volume of distribution increases, e.g. digoxin is distributed highly in myocardium and in skeletal muscle in newborn. Also salicylates are distributed in different body systems like CNS leading to salicylism.

Drugs given in neonates with jaundice can attach to albumin by competing with bilirubin and this lipid soluble bilirubin can cross BBB to cause kernicterus, e.g. sulfonamides

Drug metabolism: Preterm and full term infants and newborns have low capacity of phase 1-hydroxylation. Also plasma esterases are in low profile activity in infants due to which succinylcholine (SCH) has longer duration of action due to poor metabolism. The drug metabolizing activities of enzymes are lower in early neonatal life than later. Glucuronide conjugation reaction reaches optimal levels between 3 and 4 years of life. As neonatal have decreased ability to metabolise drugs, they have slow clearance rates and prolonged elimination half lives of many drugs, e.g. chloramphenicol induced fatal grey baby syndrome in newborn occurs as a result of decreased metabolism of chloramphenicol by glucuronyl transferase to the inactive glucuronide metabolite. Phase 11 enzyme reactions mature between 3–6 months.

Drug excretion: Renal blood flow, the glomerular filtration rate, tubular excretion is much lower in newborn than in older infants. Also, the protein binding again affects glomerular filtration because only the free drug is filtered through the glomerulus. The glomerular filtration rate and renal plasma flow increase 50% from the first day by the end of first week. By the end of the third week, the glomerular filtration is 50–60% of the adult value. The renal excretory system matures over one year of age. Hence, the drugs eliminated by kidney like aminoglycosides, penicillins, diuretics require reduced dose in neonates. After 6 months, body weight, surface area related daily doses are the same for all ages.

Adverse reactions: There can be unexpected adverse effects in children, different from those seen in adults. Chronic therapy with phenobarbital can have significant effect on learning and behaviour in children. While children are at risk with use of corticosteroid therapy (delayed development and growth suppression). Children (<2 years) are at higher risk of hepatotoxicity from valproic acid than are adults. Long-term use of aspirin causes Reye's syndrome in patients with chicken pox. Phenothiazine use can cause extrapyramidal reactions. Use of tetracyclines can cause discoloured teeth in children. Low level function of P glycoprotein transporters at birth (extrudes its substrate from inside to outside of cells) can explain the more sensitivity of neonates to opioids than older children.

Administration of some drugs has therapeutic effect in children only. Indomethacin IV injection 0.2 mg/kg followed by two doses of 0.1 mg/kg at 12- and 24-hour intervals, causes the rapid closure of patent ductus arteriosus. Infusion of prostaglandin E1 (PGE1) causes the ductus to remain open.

PEDIATRIC DOSING BASED ON AGE, WEIGHT AND SURFACE AREA

Dose = Adult dose × Age/Age + 12
Dose = Adult dose × Weight/70
Approximate dose = Surface area of child (m^2)/1. 8 × Adult dose

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Chapter
6

Geriatric Pharmacology

Society classifies everyone >65 as elderly. The important changes in drug responses occur with increasing age in most individuals. With aging, drug kinetics and pharmacodynamic effects gradually change resulting in inter-individual differences in doses needed to produce a required effect. Alternations in the quality or quantity of drug receptors may account for altered sensitivity in the elderly. Also, there are body composition alterations and changes in function of drug eliminating organs.

A. Pharmacokinetic changes: Age-dependent alterations in pharmacokinetics result from changes in:

- **Absorption:** Rate of absorption is decreased from gastrointestinal (GIT), parenteral and pulmonary routes because of decreased blood flow. Other factors that affect absorption from GIT are:
  - Decrease in gastric acid secretion.
  - Decrease in splanchnic blood flow.
  - Decreased motility.
  - Decrease in number or absolute capacity of enterocytes.
- **Distribution:** The distribution of drugs is influenced by reduction in lean body mass, serum albumin, and total body water and increase in percentage of body fat in elderly. Also, it depends upon their lipid solubility and protein binding. The body weight is reduced so that standard doses provide a greater amount of drug/kg. The body water is less and water-soluble drugs tend to be present in high blood concentration, e.g. ethanol. The plasma albumin concentrationentration is decreased giving scope for increased free drug, e.g. phenytoin, warfarin, and meperidine.
- **Metabolism:** Liver represents the major site of drug metabolism. Liver blood flow decreases causing decreased metabolism through liver and the drug appears in high concentration in plasma for longer time.

  The phase 1 reactions undergo a greater change, i.e. those carried out by mixed function oxidases (MFOs). There is altered enzyme activity which declines in phase 1 reactions. The activity of CYT P450 enzymes is decreased.

  Also, the ability of liver to carry out conjugation phase 11 reactions undergoes much smaller changes, either due to decreased liver blood flow.

  In addition, aging changes cause decline in the ability of liver to recover from injury, e.g. caused by alcohol or viral hepatitis.

CHF is more common in the elderly and can affect hepatic function by dramatically altering the liver capacity to metabolise drugs by decreasing hepatic blood flow.

Similarly, hepatic function can be impaired by severe nutritional deficiencies that occur in old age.

- **Elimination:** Decrease in blood flow to the kidneys is 1–2%/year culminating in 50% loss.

In addition, glomerular filtration rate (GFR) undergoes concomitant decrease to 50%. The decrease in GFR has considerable impact on renal clearance of number of drugs—cardiac glycosides, antibiotics and diuretics.

Age-related decline in creatinine clearance is two-thirds of the population prolonging half-life of many drugs.

Cockcroft and Gault have defined a formula for estimating creatinine clearance from serum creatinine levels as function of patient's age.

Creatinine clearance = (140 – Patient's age) × (Patient's weight)/72 × Serum creatinine.

Aging also results in reduction of activities of renal MFOs enzymes and their inducibility.

Summing up the physiological processes of renal blood flow, glomerular filtration and tubular excretion change with aging. Though there is relatively less muscle mass in the elderly age group, serum creatinine may be in the same range as in normal young adults at creatinine clearance, even 55 ml/min. Renally eliminated drugs having a small therapeutic range, e.g. aminoglycosides, digoxin, procainamide and chlorpropamide, have risk of adverse effects. Even drugs that are normally eliminated by metabolism may pose a problem through the accumulation of water-soluble metabolites which retain pharmacological activity, e.g. hydroxylated metabolites and tricyclic antidepressants.

Pharmacodynamic changes: Changes in pharmacodynamics are important factors in the elderly. Drugs that depress CNS (sedative hypnotics) produce increased effects at any given plasma concentration. There is decreased response to β-adrenoceptor stimulants. There is increased sensitivity to unwanted effects of drugs, such as hypotension from psychotropic medications, even at adjusted dose for related pharmacokinetic changes because of receptor changes and loss of hemostatic resilience. As the vital capacity and maximum breathing capacities are lessened in the elderly, the opioid drugs are also more likely to depress respiration.

Following rules can be followed for prescribing drugs to the elderly:

- Think about necessity for drugs.
- Do not prescribe drugs having serious side effects and choose alternatives.
- Choose an appropriate drug formulation: Tablet, injection, suppository or syrup is better.
- Any new symptoms should be considered as side effects or withdrawal effects.
- Take a drug history.
- Fixed dose combination is used only to help in compliance or improve tolerance or efficacy.
- When new drug is added to the present treatment, try if other drug withdrawal is possible.
- Also, monitor patient's compliance.
- Stopping a drug is as important as starting it.

The elderly cannot tolerate neuroleptics and diuretics which cause adverse electrolyte changes. Response may alter with aging to produce a greater or lesser effect than is anticipated in younger adults.

SUMMARY

Summing up, increased incidence of multiple diseases in the aged, nutritional problems, poor compliance combined with changes in pharmacokinetics and pharmacodynamics make the elderly group vulnerable to serious adverse effects and drug interactions. The disproportionately, large number of drugs that the elderly are required to take, all contribute to this outcome.

The elderly group should be prescribed medicines only when absolutely necessary for well-defined indications and at the lowest effective dose. It is necessary to monitor well-defined endpoints, do therapeutic drug monitoring and take frequent reviews of the patent's drug history, to improve the health of the elderly population. The clinical studies with a number of drug interventions have shown that chronic diseases such as hypertension and hypercholesterolemia can be treated in the elderly as much as and often more than the young. Also, the natural history of chronic diseases of the elderly, such as osteoporosis and prostate hyperplasia can be halted or reversed by appropriate drug history.

The life span of elderly patients can be prolonged and the quality of life can be nurtured by the diligent use of drugs keeping in mind the age-related pharmacokinetic and pharmacodynamic changes.

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Chapter
7

Drug Use in Pregnancy

In pregnant women, when drugs have to be given to treat a disease, they have to be carefully prescribed. Most of the drugs administered to the pregnant women can pass through the placental barrier and expose the developing embryo and fetus to their teratogenic effects. The salient factors that affect drug passage across placenta are:

A. Lipid solubility: The drug transfer across placenta is guided by lipid solubility and degree of drug ionization, e.g. thiopental used for cesarian sections, is a lipophilic drug. It crosses placenta and produces sedation in newborn. The ionised drugs like succinylcholine cross placenta slowly.

B. Molecular size: Depending on their lipid solubility and degree of ionization, drugs with molecular weights of 250–500 dalton (Da) can cross the placenta easily. Drugs with molecular weights of 500–1000 Da move across the placenta uneasily, and those with molecular weights >1000 Da cross very poorly. Hence, heparin, a high molecular weight polar anticoagulant drug is used in pregnancy instead of warfarin as it cannot pass through placenta and affect the fetus.

C. Placental transporters: Also, the placenta has drug transporters, which transfer larger molecules to the fetus, e.g. as in Rh incompatibility, maternal antibodies cross the placenta and may cause fetal morbidity.

D. Protein binding: The extent of plasma protein binding of a drug may affect the rate and the amount of drug transferred. Though for very lipid-soluble drugs, e.g. some anesthetic gases, the drug passage across placenta depends only on placental blood flow irrespective of plasma protein binding. For poorly lipid soluble and ionized drugs, their transfer is slow and will be hampered by their binding to plasma proteins. Moreover, some drugs are greatly bound to maternal plasma proteins than in fetal plasma, e.g. sulfonamides, barbiturates, phenytoin.

E. Placental and fetal drug metabolism: The placenta is a site of metabolism for some drugs passing through it. The metabolism by placenta may create toxic metabolites. Drugs after crossing the placenta pass through the umbilical vein to enter the fetal circulation. The fetal liver receives about 40–60% of umbilical venous blood flow and the remainder bypassing the liver enters the general fetal circulation.

Physiological Changes during Pregnancy

The amount of water retained at term is 6.5 litres during the whole gestational term of pregnancy. Pregnancy is defined as hypervolemic state in which occurs active retention of sodium, potassium and water. The enlarging uterus becomes increasingly vascular with the interposition of uteroplacental circulation. Blood volume is markedly raised during pregnancy to 40–50% above the non-pregnant level at 30–34 weeks. As the pregnancy progresses, there are substantial changes in physiology including fluid and tissue composition.

As vasodilation increases tissue perfusion, absorption from an intramuscular site is more efficient. There is a larger space created due to total body water accumulation to 6.5 litres, causing water-soluble drugs to distribute in it. There is increased concentration free of drugs that are bound to albumin due to fall in plasma albumin levels. The free drug can be distributed, metabolized and excreted. There is deposition of body fat increasing by 4 kg acting as a reservoir for lipid-soluble drugs. The liver metabolism is rapid leading to increased clearance of drugs, such as phenytoin and theophylline. There is more rapid loss of renally excreted drugs due to doubling of renal plasma flow, e.g. amoxicillin, the dose is twice the routine dose for systemic infections.

Pharmacodynamics

A. Maternal drug actions: Heart failure is precipitated by the increased cardiac workload of pregnancy needing cardiac glycosides and diuretics. Pregnancy-induced diabetes can occur requiring therapy for control of blood glucose.

B. Therapeutic drug actions in fetus: Phototherapy is used nowadays for the treatment of neonatal-induced hyperbilirubinemia. Earlier, phenobarbital was used to induce fetal hepatic enzymes for glucuronide conjugation of bilirubin for its excretion, to reduce the incidence of jaundice in newborns. Corticosteroids are used to stimulate fetal lung maturation. Also, in pregnant mothers, zidovudine and other anti-HIV-drug treatment decreases transmission of HIV infection from mother to fetus.

C. Fetal hazards due to maternal medication during pregnancy:

i. *Fertilization and implantation stage* (Conception to 17 days—failure of pregnancy): During early embryogenesis, the drugs reach the conceptus through the tubal or uterine secretions by diffusion. Usually, blastocyst dies or there is congenital anomaly.

ii. *During organogenesis* (Second to 12 weeks): The drug can produce gross congenital malformations and even death.

From second trimester onwards: The increased drug transfer in late months of pregnancy across the placenta is due to:

- Increased free drug available for passage.
- Increased blood flow in uteroplacental circulation
- Increased surface area of placenta
- Thinness of the placental membrane.

Following guidelines are there for using drugs:

- If the benefit is more than the potential risks which can be tolerated, only then that particular drug can be used.
- Only drugs which have been approved after clinical trials and found beneficial, must be used, using the minimum therapeutic dosage for the shortest possible duration.

Maternal Medication and Fetal or Neonatal Affection

- Dependence is produced in the fetus and newborn, by chronic use of opioids by the mother.
- Females exposed to diethylstilbesterol (DES) are at increased risk of adenocarcinoma of vagina.
- Phocomelia risk by thalidomide occurs during the fourth to seventh weeks of gestation during organogenesis because during this time arms and legs develop.
- Use of antithyroid drugs can cause goiter and mental retardation.
- Use of oral antidiabetics can cause abnormalities in the eyes, CNS, skeletal systems and neonatal hypoglycemia.
- Use of aminoglycosides can cause deafness.
- Use of long-acting sulfonamides can cause jaundice and kernicterus.
- Hemolysis occurs in newborn with nitrofurantoin in presence of glucose-6-phosphate dehydrogenase deficiency.
- Vitamin D can cause cardiopathies, hypercalcemia and mental retardation.
- Chronic alcohol consumption can cause IUGR and preterm labour.

Treatment of Common Medical Illnesses during Pregnancy

- **Anemia in pregnancy:** During the second half of pregnancy, there is an increased demand for iron due to increase in plasma volume, RBC volume and Hb mass. A balanced diet rich in vitamins, iron and proteins is required. The specific therapy consists of oral iron preparations as ferrous sulfate, ferrous fumarate or ferrous succinate. Intramuscular (IM) therapy consists of:
  - Iron dextran (imferon)
  - Iron sorbitol citric acid complex (jectofer).
  - The injections are painful. The parenteral therapy is given when there is intolerance to oral iron or in severe anemia. The expected rise in Hb after therapy is 1–1.4 g/100 ml per week.
  - Folic acid supplementation 5 mg/day during pregnancy decreases the incidence of neural tube anomalies, e.g. spina bifida.
  - Heparin IV is given as anticoagulant in early pregnancy. Warfarin can be given as an anticoagulant in late pregnancy orally.
  - B2-selective agonists, corticosteroids are to be given in bronchial asthma and dextromethorphan for cough.
  - For anxiety disorders and insomnia, diazepam is given.
  - Primary hypothyroidism occurs in pregnancy due to thyroid autoimmunity mostly. Generally, therapy is started with 2–2.4 µg/kg /day. The maintenance dose is 75 and 150 µg of L-thyroxine per day. The serum TSH should be repeated every 4–6 weeks.
- For diabetes, human insulin is the preferred drug. Insulin therapy is given at a postmeal plasma glucose level of more than 140 mg % even on diet control. Before meals, glycemic goals should be around 90 mg/dl not exceeding 120 mg/dl 2 hours after meals.
- For fever and headache, take paracetamol 500 mg QID.
- For hypertension, labetolol, hydralazine and alpha methyl dopa. The dose of methyldopa is 250–300 mg, 2–3 times as needed, maximum dose 3000 mg/day and the dose of labetolol 100 mg twice daily, increase 100 mg twice daily every 2–3 days as needed, maximum dose 2400 mg/day.

- For nausea and vomiting, antacids preferred. For reflux esophagitis, antacids are preferred.
- For epilepsy, lamotrigine and levetricetam is the recommended drug. The dose of lamotrigine in pregnancy is 150–500 mg, BD. Levetiracetam 0.5 g BD, progressively increased to 1 g BD.
- For active TB during pregnancy, all first line oral drugs given for 9–18 months.
- Asymptomatic bacteriuria—amoxycillin 500 mg, TDS; nitrofurantoin—100 mg BD; cephalexin 500 mg, TDS.

Pregnant women should have a detailed ultrasound scan at 20 weeks of gestation in order to identify any fetal defects. Drug concentration should be monitored every 2 weeks after delivery until it is clear how quickly the pharmacokinetics of the drug can be returning to pre-pregnancy values. The dose should be adjusted accordingly. Prepregnant dose requirements usually can be resumed by 6 weeks postpartum.

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Chapter
8

Drug Use in Lactation

Lactation period is the most important period of a woman's life. It requires careful administration of drugs. As most drugs administered to lactating women are detectable in breast milk, careful administration of drugs is essential. Actually, all drugs present in maternal plasma will be reaching milk. Drugs are transported to milk from maternal plasma by diffusion. Lipid solubility, acid–base characteristics, protein binding profile of the drug regulates its entry into breast milk. Some drugs who attain more than 50% of maternal plasma concentration in infant plasma, alternative cow's milk should be given. Breast-feeding is stopped when unsafe drugs are perceived by the nursing mother, e.g. sedative hypnotic diazepam can prolong sleeping time of the infant. The lactating mother should optimally take a safe drug 30–60 minutes after nursing and 3–4 hours before the next milk feed to the child. Here are few examples of effect of drug intake in lactating mothers on feeding infants:

- Most antibiotics administered to lactating mothers can be detected in breast milk. Tetracycline concentration in breast milk is approximately 70% of concentration present in maternal plasma and poses permanent tooth staining risk in the infant.
- Chloramphenicol should be avoided during lactation as it causes bone marrow suppression
- Most sedatives and hypnotics reach concentration in breast milk sufficient to produce a pharmacological effect in some infants. Lethargy, sedation and poor suck reflexes in the infant can be produced at hypnotic doses of barbiturates by the mother. Diazepam can have a sedative effect on nursing infant.
- Opioids such as heroin, methadone and morphine produce narcotic dependence by entering breast milk.
- Li enters breast milk in sufficient amounts to cause toxicity—lethargy, restlessness, feeding, problem, abnormal growth and development. Breastfeeding is stopped if the mother is taking Li.
- Radioactive substances can cause thyroid suppression in infant and increase the risk of thyroid cancer. After large doses, breastfeeding is contraindicated and should be withheld for days to weeks after small doses.
- **TB in mothers:** Breastfeeding can be continued while on treatment with all anti-TB drugs. The mother should ge given full regimen while monitoring the baby. After ruling out active

TB, the infant should receive BCG vaccination and 6 months isoniazid preventive treatment. Breastfeeding by HIV-positive mother is contraindicated because it carries substantial risk of transmission to the infant.

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Chapter
9

Drug Interactions

When two or more drugs are given together for treatment of a disease, they may interact with one another and this is called drug interaction. One drug's response may be altered by prior or concomitant administration of another drug. The interaction may cause failure of treatment, additive or synergistic pharmacological effect, or a fatal toxic effect. Drug interactions are more predictable and presentable than adverse drug reactions as they have a specific time course in terms of onset and duration.

Drug interactions may be due to any one of the two important categories. First one is pharmacokinetic drug interaction, in which the drug concentration is altered at the site of action by absorption, distribution, metabolism or excretion. Second one is pharmacodynamic interactions, which occur at the level of target site, exerting synergism or antagonism. Adverse drug interactions can occur *in vitro*, e.g. heparin should not be infused with basic drugs in the infusion fluid and *in vivo*, e.g. one drug may alter the pharmacokinetics of second drug.

Important drug interactions clinically become more likely with drugs with following characteristics and conditions:

- Drugs having steep dose response curve and a small safety range as small substantial changes at the target site, e.g. receptor or enzyme caused substantial changes in effect, e.g. digoxin or lithium.
- Drugs either enzyme inducers or inhibitors.
- Drugs following saturable metabolism (zero order metabolism), when constant elimination occurs regardless of the plasma concentration, e.g. phenytoin, theophylline.
- Long-term use of drugs, where precise plasma concentrations are required, e.g. oral contraceptives, antiepileptic drugs, cardiac antiarrhythmic drugs.
- Polypharmacy in severely ill patients.
- Patients with significant liver or kidney dysfunction.
- Elderly suffering with multiple pathological conditions and receiving several drugs concurrently.

A. Drug Interaction due to Pharmacokinetic Mechanisms

a. Absorption: GIT absorption of many drugs is influenced by concurrent use of other agents having large surface area that bind or chelate, alter gastric pH, alter GIT motility, affect transport proteins such as *p*-glycoprotein.

- Atropine decreases gastric emptying and decreases intestinal absorption of other drugs.

- Prokinetic drugs that hurry gastric emptying increase GIT absorption.
- Milk, antacids and iron preparations form chelates with tetracyclines and decrease their absorption.
- Sucralfate decreases phenytoin levels due to inhibition of its GI absorption. Such drug interactions could be minimized by administering 2 drugs with a gap of 2–3 hours so that they cannot come in contact with each other in the GIT.
- H2 blockers and PPIs decrease ketoconazole absorption because they decrease gastric acidity which promotes dissolution and absorption of ketoconazole.
- An addition of epinephrine to local anesthetic injection slows down the systemic absorption of local anesthetics and prolongs its duration of effect by providing local vasoconstriction.

b. Distribution: The distribution is altered by competing with plasma protein binding and displacing from tissue binding sites, e.g. drugs like quinidine, verapamil, amiodarone displace digoxin from tissue-binding sites to increase its bioavailability. The sulfonamides displace bilirubin in neonates from its protein-binding sites causing kernicterus.

c. Metabolism: The hepatic cytochrome P450 iso-enzyme system causes most of the known drug interactions. CYT P450 is a group of heme-containing isoenzymes located on the membrane of the smooth ER (endoplasmic reticulum) mainly in liver and intestinal tract. It metabolises endogenous substances (steroids, hormones, prostaglandins, lipids, fatty acids) and involved in detoxification of exogenous compounds (especially after oral ingestion). Cyt P450 isoenzymes are used as substrates by many drugs for their metabolism. Drugs can inhibit or induce metabolism of other drugs given concurrently by competing for metabolism for available P450 isoenzyme substrates. Barbiturates, phenytoin, rifampin, troglitazone can induce cytochrome isoenzymes in liver and small intestine. The drug metabolising enzymes can be induced or inhibited leading to therapeutic failure or increased effect, respectively.

- Enzyme induction: Cytochrome P450 isoenzymes induction by any substance causes increased synthesis of that isoenzyme, resulting in increased metabolism and hepatic clearance of all substrates through that specific pathway, e.g. rifampicin, phenobarbital is capable of inducing different isoenzymes. Some drugs like carbamazepine, imipenem prompt time-dependent induction by an autoinduction process caused by increased synthesis of that isoenzyme leading to increased metabolism and hepatic clearance of all substrates through that specific pathway. Rifampin as a microsomal inducer increases CYT P450, CYP1A2, CYP2AC subfamily. It induces metabolism of many drugs like warfarin, oral contraceptives, corticosteroids, sulfonylureas, steroids, HIV protease inhibitors, theophylline, metoprolol, fluconazole, ketoconazole, clarithromycin, phenytoin. Rifampicin causes contraceptive failure. Alcohol consumption and smoking induce CYP2E1 and CYP1A2, respectively. Terfenadine and asmetizole are prodrugs that undergo extensive hepatic metabolism to active and inactive metabolites by CYP3A subfamily. Both terfenadine and asmetizole can cause torsades de pointes, a life-threatening cardiac arrhythmia.
- Enzyme inhibition: One drug may inhibit the metabolism of another drug causing increased levels of slowly metabolized drug and prolongation of potentiation of its pharmacological effects, e.g. cimetidine. Theophylline metabolism is inhibited by erythromycin by inhibition of CYP3A4. Erythromycin and clarithromycin are potent inhibitors of CYP3A4 inhibiting the metabolism of drugs, e.g. terfenadine, asmetizole, cisapride, theophylline.

- Ketoconazole and itraconazole are inhibitors of CYP3A4 and have shown to cause increased QT interval and fatal torsade's de pointes when used with asmetizole or terfenadine.
- **Excretion:** An active drug's renal excretion can also be affected by concurrent drug therapy. Other drugs that affect urinary pH, influence the renal excretion of certain drugs that are weak acids or weak bases, due to changes in ionization of drug. Some drugs are eliminated by active secretion into renal tubules.
- The changes in glomerular filtration rate, tubular reabsorption and tubular secretion affect renal drug clearance, e.g. the tubular secretion of penicillins and cephalosporins is blocked by probenecid and their action is prolonged.
- Sodium bicarbonate alkalises urine and increases excretion of acidic drugs, e.g. aspirin and barbiturates.
- Ammonium chloride or ascorbic acid acidifies urine and increases excretion of basic drugs such as morphine.
- Thiazide diuretics elevate blood glucose levels and may counteract blood sugar lowering effect of oral hypoglycemic drugs.
- The active tubular secretion of some drugs is by means of P glycoprotein, organic anion transporters (OATP), organic cation transporters (OCT). P glycoprotein effluxes drugs like digoxin, cyclosporine, dabigatran, daunorubicin and tacrolimus. The plasma concentration of these drugs can be increased by inhibiting P glycoprotein. Probenecid has high affinity for tubular organic anion transporting polypeptide (OATP) and decreases excretion of penicillin. OATP and OCT transport processes can transport their substrates from blood to tubular fluid and vice-versa.

B. Drug Interaction due to Pharmacodynamic Mechanisms

When administering drugs with similar pharmacological effects, an additive or synergistic response is usually seen leading to supra-additive effect. If the two drugs have opposite pharmacological effects, it leads to antagonism (leading to decreased effects) known as pharmacodynamic interactions.

Additive effect: The effect of two drugs add up. Amlodipine + atenolol as antihypertensive.

Supra-additive effect: The effect of combination is greater than the individual effect of the components, e.g. sulfamethoxazole + trimethoprim. Both are bacteriostatic drugs but the combination becomes bactericidal.

Combined toxicity: The use of two or more drugs in combination can produce toxic effects on the same organ, causing organ damage. The concurrent administration of two nephrotoxic drugs can produce kidney damage. Loop diuretics increase the ototoxicity of aminoglycosides. Use of two CNS depressants, e.g. BZPs and antihistamines may cause excess sedation. Metoclopramide increases extrapyramidal side effects of phenothiazines. Potassium sparing diuretics and angiotensin-converting enzymes (ACEs) given together cause severe hyperkalemia.

Antagonism: CNS-stimulant drugs and CNS-depressant drugs antagonize each other's action.

Drug–food interaction: Some of the drug–food interactions are of significant importance.

1. Monoamine oxidase inhibitors (MAOIs) cause hypertensive reactions in person taking tyramine rich food, e.g. matured cheese, red wines.

2. Grape fruit and oranges inhibit CYP3A4 isoenzyme system and increase bioavailability of drugs like indinavir, saquinavir and midazolam.
3. A rich protein diet produces acidic urine which promotes excretion of basic drugs. Low protein diet provides alkaline urine which promotes excretion of acidic drugs, e.g. aspirin.
4. Food, orange juice, coffee, tea markedly decrease the bioavailability of alendronate. Hence, the drug is administered empty stomach with plain water only.

Drug Herbal Interactions

Gingko biloba increases the bleeding tendency with concurrent use of antiplatelet and anticoagulant drugs.

St. John's wart causes phototoxicity when used with tetracyclines, sulfonamides and proton pump inhibitors.

Administration of garlic/ginger with anti-coagulant and anti-platelets should be avoided because of risk of bleeding.

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Chapter 10

Treatment of Alcohol Use Disorder

Alcohol consumption is responsible for 5.9% of all causes of death and for 5.1% of all causes of disease in the world. The chronic use of alcohol can lead to the onset of an alcohol use disorder (AUD) as defined in the new version of the Diagnostic and Statistical Manual of Mental Disorders, which, with respect to previous editions, has eliminated the stigmatizing terms of abuse and dependence. AUD includes acute alcohol intoxication (AAI), post-alcohol hangover, alcohol withdrawal syndrome (AWS) with life-threatening complications, convulsions or delirium tremens.

ACUTE ALCOHOL INTOXICATION

Acute alcohol intoxication is an intercurrent, potentially transitory condition that is caused by drinking a considerable amount of alcohol.

Symptoms

- Behavioural alterations such as euphoria, dysphoria, social disinhibition, sleepiness, belligerence and aggressiveness and as the blood-alcohol concentration increases, lethargy, stupor and coma. A transitory memory deficit may occur.
- Several metabolic alterations including hypoglycemia, lactic acidosis, hypokalemia, hypomagnesemia, hypoalbuminemia, hypocalcemia, and hypophosphatemia.
- Occasionally leads to muscular complications; these may include acute myopathy characterized by pain, muscular flaccidity and rhabdomyolysis with high blood levels of creatinine phosphokinase (CPK) and myoglobinuria: Severe cases are potentially lethal due to the onset of hyperkalemia and acute renal insufficiency due to rhabdomyolysis.
- Cardiovascular effects including tachycardia, peripheral vasodilatation, and volume depletion may appear; these features can contribute to the induction of hypothermia and hypotension. One possible cardiovascular effect is 'holiday heart syndrome', characterized by atrial or ventricular tachy-dysrhythmias and new-onset atrial fibrillation after acute alcohol ingestion.
- Gastrointestinal effects include nausea, vomiting, diarrhea, abdominal pain secondary to gastritis, peptic ulcer, and pancreatitis. AAI can induce acute alcoholic hepatitis (AAH), usually in subjects with chronic and heavy alcohol use or patients present with alcoholic liver cirrhosis.

Treatment

- In the case of mild-to-moderate AAI, no drugs are generally necessary, but vital functions should be monitored, liquids administered in the case of dehydration, and the patient kept under observation for the onset of alcohol withdrawal symptoms.
- In the case of severe AAI with coma, it is important to support ventilation mechanically, identify any additional causes of coma and, if necessary, correct hypoglycemia with 5% glucose solution, correct hydroelectrolyte imbalance and acid–base balance, administer vitamin B and vitamin C supplements, perform gastrolavage and administer activated charcoal only within 2 h of drinking a considerable amount of alcohol.
- In the case of the simultaneous use of other sedative drugs, specific antidotes should be administered, naloxone (0.4 mg, IV or IM repeated, if necessary, every 30 min) for opioids use and flumazenil (0.2 mg, repeated, if necessary, every minute up to 3 mg) for benzodiazepine (BDZs) use.
- The administration of drugs (reduced glutathione, 600 mg, IV or S-adenosylmethionine, 400 mg, IV or metadoxine 900 mg, IV diluted in 500 cc of saline or electrolyte solution in a single daily administration for 2–3 days) that reduce the blood alcohol and acetaldehyde concentrations leads to a more rapid resolution of the symptoms.
- To resolve the symptoms of alcohol hangover more rapidly; fruit and fruit juice, sleep and physical rest, anti-acid drugs, acetylsalicylic acid, and caffeine may be helpful.

ALCOHOL WITHDRAWAL SYNDROME (AWS)

AWS is defined as: (a) cessation or reduction in alcohol use that has been heavy and prolonged; (b) two (or more) of the following, developing within several hours to a few days: autonomic hyperactivity, increased hand tremor, insomnia, nausea or vomiting, transient visual/auditory/tactile hallucinations or illusions, psychomotor agitation, anxiety, and generalized tonic clonic seizures.

The abrupt reduction or suspension of alcohol intake in a subject with a severe AUD is receptorially characterized by reduced gamma-aminobutyric acid (GABA) activity and increased glutamatergic activity with hyperexcitability and development of withdrawal symptoms.

The symptoms of AWS generally appear 6–8 h after the last drink and reach a peak in the subsequent 24–72 hours. The first symptoms of AWS are tremor, nausea, vomiting, insomnia, agitation, delirium and visual (macro and micro-zoopsias) or auditory hallucinations (voices), or other perception disorders. These may be compounded by symptoms of autonomic hyperactivity: Red face, tachycardia, profuse sweating, hypertension and hyperthermia. AWS can progress towards its most dramatic complication, delirium tremens (DTs).

In particular, DTs is a clinical condition characterized by a cognitive and attention disorder with rapid and fluctuating onset, sometimes also accompanied by hallucinations. In 80% of cases, DTs abates within 72 hours if treated pharmacologically, and the patient often does not remember the occurrence.

Treatment

- The most appropriate non-pharmacological approach in the treatment of AWS is hydration (if necessary) and the administration of vitamin supplements (thiamine) to prevent the onset of Wernicke's encephalopathy. Parenteral dose 250–300 mg BD for 3–5 days followed by oral dose 250–300 mg/day.

- Benzodiazepines (BDZs) are the gold standard for the pharmacological treatment of AWS since they are the only drugs that prevent the onset of its serious complications (delirium, tremens and seizures).
- A fixed-schedule regimen is highly effective and its use is preferable in patients at risk of developing a severe form of AWS or in patients with a history of convulsions and DTs; however, patients must be kept under strict surveillance due to the risk of excessive sedation or respiratory depression.
- A symptom-triggered regimen with BDZs with a shorter half-life (lorazepam and oxazepam) could be preferable for the treatment of AWS in elderly patients and in those with acute alcoholic hepatitis and advanced liver cirrhosis in order to achieve the clinical effect with a minimal administration of drugs, avoiding an accumulation of the same drugs too.
- Outpatient treatment is appropriate in patients with mild or moderate AWS with or without complications (DTs and seizures). Alfa-2-agonists, beta-blockers, and neuroleptics should only be administered in association with BDZs when the latter are not effective in controlling specific persisting symptoms of AWS.
- GABA-ergic medications such as sodium oxybate and clomethiazole, and dopaminergic antagonist drugs such as tiapride are approved and may be a further pharmacological option for the treatment of moderate forms of AWS.

Methyl Alcohol (Wood Alcohol) Poisoning

It is an uncommon extremely hazardous poisoning. It occurs via oral ingestion or adulterated liquors. It may cause severe metabolic disturbances, blindness, permanent neurological dysfunction and death. Metabolic acidosis occurs requiring administration of bicarbonate and assisted ventilation.

Antidote therapy is ethanol administration through nasogastric tube—0.7 ml/kg followed by 0.15 ml/kg/hr or fomepizole—15 mg/kg, IV, followed by 10 mg/kg, 12 hourly. Both the drugs inhibit methanol metabolism by inhibiting alcohol dehydrogenase. Toxic metabolite formic acid is not formed.

- Hemodialysis is another option.
- Calcium leucovorin, 50 mg IV, 6 hourly oxidises blood formate.

SUMMARY

Alcohol poisoning

Alcohol is a CNS depressant

Stage 1: Drowsy

Stage 2: Pupillary dilation stage

Stage 3: Hallucination

Stage 4: Intoxication

Gastric lavage is done and serum ethanol levels are checked. Dextrose injections are not given because of risk of Wernick's encephalopathy or Korsakoff's psychosis. Thiamine with other multivitamins is given. Dialysis with fomepizole is done.

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Chapter
11

Treatment of Epilepsy

Epilepsy affects 1% of the human population and is a chronic disorder characterized by recurrent seizures. There is abnormal discharge of cerebral neurons due to hyperexcitability of neurons which fire bursts of action potentials that propagate in a **synchronous manner** to other brain structures.

Epileptic seizures are classified based on the clinical features of seizures and associated EEG findings according to International Classification of Epileptic Seizures (ICES, in three main types: Partial, generalized, and unclassified.

1. **Partial seizures** start from a local point and limited to specific area of the cerebral cortex.
   a. **Simple partial seizures** cause motor, autonomic or psychic symptoms without alteration of consciousness.
   b. **Complex partial seizures** have localized seizure activity, accompanied by transient loss of consciousness.
   c. **Partial seizures with secondary generalization** can spread to involve both cerebral hemispheres and may produce a generalized seizure.
2. **Generalized seizures have onset** from both cerebral hemispheres simultaneously. These are of following types:

   Absence seizures (petit mal) involve sudden brief lapses of consciousness without loss of postural control. The seizure typically lasts for only seconds and there is no postictal confusion. The patient may stare into space for few seconds accompanied by lip smacking, eyelid fluttering and chewing movements.

   Generalized, tonic–clonic seizures: Formerly known as grand mal seizure. They are found approximately in 20% of all persons with epilepsy. These can be triggered by hypoglycemia, high fever or stroke. The usual stages are—prodromal phase, aura, ictal phase, tonic spasm of all body muscles, clonic jerking followed by prolonged sleep and depression of all CNS functions. The person loses consciousness and the seizure lasts one to three minutes.

   Atonic seizures: There is sudden loss of muscle tone lasting 1 to 2 seconds causing the person to fall to the ground or drop what they are holding.

   Myoclonus is characterized by sudden brief jerks or twitchings of the arms and legs. It can be a sudden and brief muscle contraction that may involve one part of the body or the entire body.

3. **Unclassified seizures** that occur in neonates and infants due to differences in neuronal function and connectivity in the immature brain, e.g. neonatal seizures, infantile spasms.

CAUSES OF EPIEPSY IN DIFFERENT AGE GROUPS

In neonates: Perinatal hypoxia and ischemia, intracranial hemorrhage and trauma, acute CNS infection (bacterial and viral meningitis), metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency, drug withdrawal, developmental disorders (acquired and genetic) and genetic disorders.

In infants and children: Febrile seizures, genetic disorders (metabolic, degenerative, primary epilepsy syndromes), CNS infections, developmental disorders (acquired and genetic), trauma, idiopathic.

In adolescents: Trauma, genetic disorders, brain tumors, illicit drug use.

In young adults: Trauma, alcohol withdrawal, illicit drug use and idiopathic.

In old adults: Cerebrovascular disease, brain tumors, alcohol withdrawal, metabolic disorders, Alzheimer's disease and idiopathic.

CLASSIFICATION

Barbiturates: Phenobarbitone, mephobarbitone, deoxybarbiturates—primidone

Hydantoins: Phenytoin, methatoin and ethatoin

Iminostilbene: Carbamazepine, oxycarbamazepine

Succinimide: Ethosuximide, methsuximide

Aliphatic carboxylic acid: Valproic acid

Benzodiazepines: Clonazepam, clobazam, diazepam

Newer drugs—Lamotrigene, garbapentin, vigabatrin, tiagabine, zonisamide, topiramate and felbamate.

Antiepileptic Drugs' Mechanism of Action (Fig. 11.1)

1. Maintain inactivated state of sodium channel, e.g. phenytoin, carbamazepine, lamotrigine, sodium valproate, topiramate and zonisamide
2. Block Ca^{2+} T current, e.g. ethosuximide, sodium valproate
3. Act via gamma-aminobutyric acid-A (GABA-A) mediated CL-channel complex—benzodiazepene receptors, e.g. clonazepam
4. Increase GABA concentration, e.g. sodium valproate
5. Act on barbiturate receptors, e.g barbiturates
6. Blockade of N-methyl-D-aspartate (NMDA) receptors—lamotrigine

TREATMENT OF EPILEPSY

Depending upon different types of seizures and their etiology, treatment is individualized. Also difference in efficacy and toxicity of anti-epileptic medications for each patient decides the treatment. Treatment is under following guidelines.

1. **Treatment of underlying condition:** If cause is metabolic disturbance, e.g. abnormality of serum electrolytes or glucose or drug, correct the cause of seizure.
2. **Avoidance of the precipitating factors:** Lack of sleep, alcoholic, overstress.

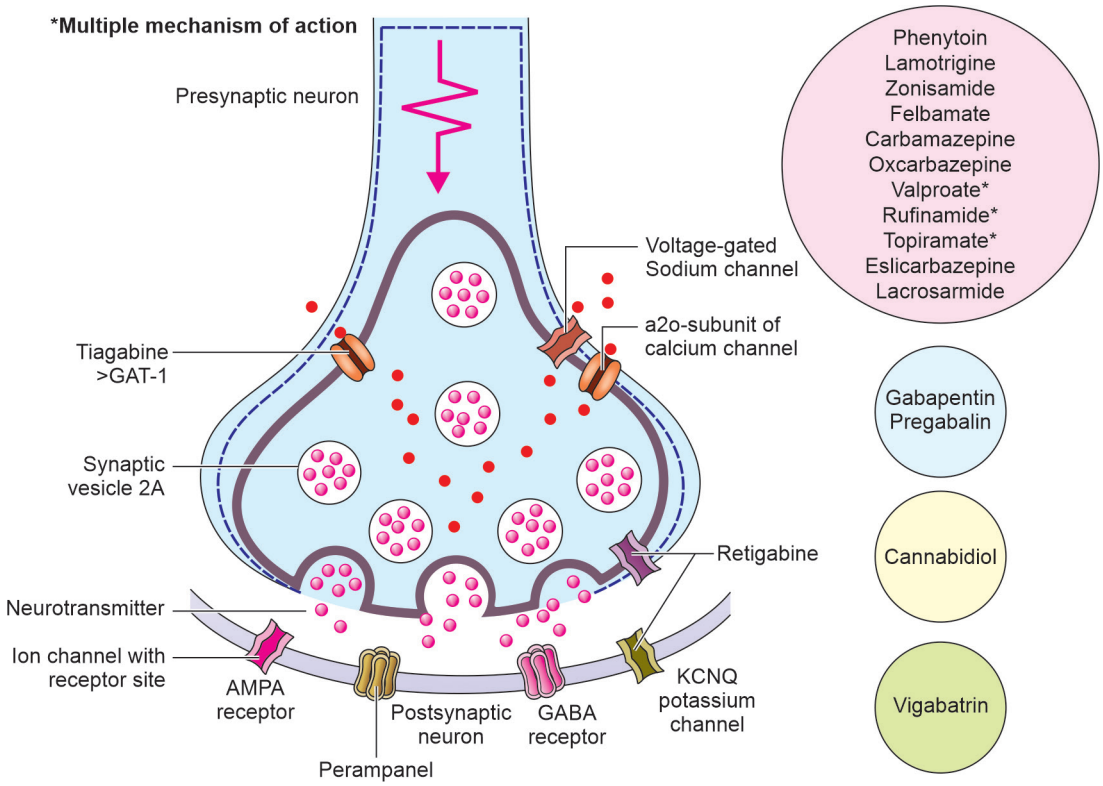

Fig. 11.1: Mechanism of action of antiepileptic drugs

3. **Antiepileptic drug therapy:** The treatment is aimed to prevent seizures without causing any serious adverse effects. Treatment is started with a single medication and an easier dosing schedule in any patient with recurrent seizures of unknown etiology or known cause that cannot be reversed. Also, in patient with single seizure due to identified lesion—CNS tumor, infection and trauma, treatment should be done.
4. **Initiation and monitoring of therapy:** Most anticonvulsants should be administered slowly to minimize side effects. Therapeutic drug monitoring is very useful in establishing the initial dosage schedule, especially for phenytoin where a small increase in dose may lead to disproportionate rise in plasma drug concentration. About 25% patients do not achieve seizure control because of unacceptable side effects, hence 2 or more drugs are concurrently used. If seizures continue despite gradual increase to the maximum tolerated dose, it is necessary to switch to another antiepileptic drug. This is done by maintaining the patient on the first drug while a second drug is added. The dose of the second drug should be slowly increased to decrease seizure frequency without causing toxicity. Once the seizures slow down, first drug can be gradually withdrawn. Optimization of the second drug dose is done based on seizure response and side effects.
5. **When to discontinue therapy:** The drug therapy can be discontinued gradually in 70% children and 60% adults who have seizures completely controlled with antiepileptics. Clinical studies suggest following patient profile for drug withdrawal:
   - There is total treatment control of seizures for 1–5 years.
   - Single seizure—partial/generalized.

- Patient has normal neurological examination including intelligence.
- Normal EEG.

Withdrawal therapy can be attempted after 2 years in a patient who meets the above criteria. The dose can be tapered gradually over 2–3 months. Most recurrences occur in the first 3 months after discontinuation of therapy.

6. **Treatment of recurrent epilepsy:** One-third patients do not respond to single drug therapy to control seizures. So, 2 of the first-line drugs—carbamazepine, phenytoin and valproic acid—are given in combination. If these drugs fail, one of new drugs—lamotrigine or gabapentin is introduced. Patients with myoclonic seizures have good response to valproic acid and clonazepam. Absence seizures respond to valproic acid and ethosuximide.

Surgical treatment of refractory epilepsy: 20% patients with epilepsy do not recover with medical therapy. Here, surgical treatment is advised to decrease seizure frequency and to provide complete seizure control. Most common surgery for temporal lobe epilepsy is temporal lobectomy or more limited removal of the underlying hippocampus and amygdala. Multilobectomy is done for patients with several seizure foci.

COMMONLY USED ANTIEPILEPTICS

Phenytoin: It is used for treatment of generalized tonic-clonic (GTC) (grand mal), complex partial (psychomotor, temporal lobe) seizures and perioperative neurosurgery. A more soluble polymer of phenytoin—fosphenytoin is available for parenteral use and is well-absorbed and can be given in dextrose infusion. Phenytoin loading dose is 800 mg in 500 ml normal saline over half a hour followed by maintenance dose of 100 mg TDS injections. Adverse effects are ataxia, incoordination, confusion, osteomalacia, facial coarsening, skin rash. The most common side effects in children receiving long-term therapy are gum hypertrophy, hirsutism in young females. Patients may experience altered level of consciousness and cognitive changes at higher doses.

Valproic acid: It has good efficacy against absence seizures and myoclonic seizures. Also, used for treating generalized tonic-clonic epilepsy and for complex partial seizures. The therapeutic levels of valproate range from 50 μg/ml to 100 μg/ml in most patients. The starting dose is 10 to 15 mg/kg per day, and increased by 5 to 10 mg/kg per week to achieve optimal clinical response. The dangerous adverse effects can be hepatotoxicity, teratogenicity and pancreatitis. Other side effects are weight gain, increase in appetite, GIT distress, thrombocytopenia, tremors and alopecia.

Carbamazepine: It is used to treat generalized tonic-clonic seizures and complex partial seizures. Initial dose is 400 mg/day orally, increase the dose every week up to maximum 1200 mg/day. Its half-life is 13–17 hrs. The therapeutic range is 4–12 μg/ml. The pediatric dose is 15–25 mg/kg/day. Adverse effects are ataxia, diplopia, vertigo, aplastic anemia, leucopenia, GIT irritancy, hepatotoxicity, water retention, hyponatremia, erythematous rash.

Oxcarbamezepine: It is used in partial seizures. Dosage starts with 600 mg/day, increase weekly to 2400 mg/day, given twice daily. Its active metabolite (10 monohydroxy metabolite) has half-life of 10–17 hrs. Therapeutic range is 6–12 μg/ml. Fatigue, ataxia, dizziness, diplopia, headache, and systemic toxicity are the adverse effects.

Phenobarbital: It is used in both GTC and partial seizures. The dose is 60–180 mg/day and half-life is 90 hrs. The loading dose is 10–20 mg /kg to achieve therapeutic blood concentration range of 10–20 µg/ml. Adverse effects are sedation, ataxia, confusion, depression and skin rash.

Ethosuximide: It is indicated for absence (petitmal) seizures. With dosage of 750–1500 mg/day, the therapeutic levels of 60–100 µg/ml can be achieved in adults. Gastric distress, nausea, vomiting, skin rash like Stevens-Johnson syndrome are common dose related adverse effects.

Levetiracetam: It is used as add on therapy for partial onset seizures, myoclonic seizures, primary GTC seizures. The initial dose is 1000 mg/day, in two divided doses, additional incremental dosing by 1000 mg/day every 2 weeks to a maximum recommended daily dose of 3000 mg. Half-life is 6–8 hrs. Adverse effects are somnolence, asthenia, and dizziness.

Topiramate: It is an adjunctive therapy for partial onset seizures or GTC seizures, seizures associated with Lennox–Gastaut syndrome. It blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter GABA at GABA-A receptor. Usual dose is 200–400 mg/day. Its half-life is 20–30 hrs. Adverse effects are somnolence, dizziness, fatigue, paresthesia, and urolithiasis.

Lamotrigine: It is administered as add-on therapy in partial onset seizures, GTC seizures, absence seizures, myoclonic seizures, Lennox-Gestaut syndrome. The dose is 100–300 mg/day in two divided doses. Its half-life is 24 hrs. Adverse effects are dizziness, diplopia, sedation, ataxia, and rash.

Lacosamide: It is administered as add-on therapy for partial onset seizures. It causes slow inactivation of voltage-gated sodium channels leading to inhibition of repetitive neuronal firing due to stabilization of neuronal membranes. Given oral or IV. The initial dose is 50 mg twice daily (100 mg/day). The dose is increased by 100 mg/day, given as two divided doses up to the recommended maintenance dose of 200 to 400 mg/day, depending on patient's response and tolerability. Common side effects are nausea, vomiting, dizziness, drowsiness, blurred vision, tiredness, disequilibrium, difficult gait, tremor, or memory problems.

Gabapentin: It is used as additive therapy for partial seizures. The dose is 900–2400 mg/day. Its half-life is 6–8 hrs. Adverse effects are sedation, dizziness, ataxia, fatigue and GIT irritation.

Felbamate: It is administered only to patients failing to recover by first line and alternatives therapy or in severe epilepsy with substantial risk of liver failure and/or aplastic anemia. It is effective in focal onset, Lennox–Gestaut syndrome. The dose is 2400–3600 mg/day in two divided doses. Side effects are sleeplessness, dizziness, sedation, headache, hepatic failure aplastic anemia, hepatic failure, weight loss, GIT irritation.

Vigabatrin: It is recommended as additive therapy in complex partial seizures resistant to alternative treatments and in whom the potential benefit compromises the risk of visual impairment. It acts through irreversible inhibition of GABA transaminase. Starting dose is 500 mg BD, can be increase up to 3 g/day on weekly basis. Half-life is 6–8 hrs and eliminated primarily via kidney. Renal impairment needs dose adjustment. Adverse effects are dizziness, weight gain, agitation, and confusion, long-term use causes vision loss.

Tigabine: It is given as addon therapy in partial seizures. Initial dose is 4 mg /day, increase on weekly basis to 32 mg/day in three divided doses. Adverse effects are nervousness, dizziness, difficulty in concentrating, depression, and rash.

Zonisamide: It is used in complete generalized seizures, partial seizures, infantile spasms. Initial dose is 100 mg/day dose, increase after each 2 weeks up to 400 mg/day. Half-life is 1–3 days. Side effects are drowsiness, cognitive impairment, skin rash.

Benzodiazepines (BZDs): Enhance action of GABA through GABA-A receptors at BZP-binding site. The side effects of BZDs are sedation, tolerance.

Diazepam has half-life of 1–2 days.

Lorazepam given IV is more effective and longer-acting than diazepam. It is used in emergency treatment of status epilepticus.

Clonazepam is longer-acting drug with efficacy against absence seizures, myoclonic seizures and infantile spasms. Dose in adults is up to 1.5 mg/day and dose in children is 0.01–0.03 mg/kg/day.

Nitrazepam is used for infantile spasms and myoclonic seizures.

Clobazam is used in absence, atypical, myoclonic seizures, is less sedative than BZDs, available in the United States (US). The dose is 0.5–1 mg/kg/day.

ANTIEPILEPTICS OF CHOICE

PARTIAL SEIZURES

First-line drugs: Carbamazepine, oxcarbazepine, phenytoin, valproic acid. Alternatives—levetiracetam, topiramate, gabapentin, phenobarbital, primidone, felbamate, vigabatrin and lacosamide.

GENERALISED TONIC-CLONIC SEIZURES

First-line drugs: Valproic acid, phenytoin, lamotrigine, topiramate, alternatives—clonazepam, phenobarbitone, carbamazepine and oxcarbazepine

Myoclonic seizures: First-line drug—valproic acid, alternative—clonazepam

Atonic seizures: First-line drug—valproic acid, alternative—clonazepam

DRUG INTERACTIONS

Phenytoin: Isoniazid (INH), cimetidine increase its levels. Level is decreased by enzyme inducing drugs. Valproate displaces protein bound by inhibiting phenytoin metabolism. Phenytoin increases its plasma levels. Phenytoin induces microsomal enzymes causing metabolism of number of drugs.

Carbamazepine: It is an enzyme inducing drug. Phenobarbitone and phenytoin induce its metabolism and *vice versa*.The metabolism of carbamazepine is inhibited by erythromycin.

Valproic acid: The plasma level is decreased by enzyme inducing drugs. Valproate inhibits metabolism of phenytoin at lower doses by displacing phenytoin from binding to plasma proteins. The metabolism of phenobarbitone, and lamotrigine is inhibited by valproate.

Phenobarbitol: Its plasma level is increased by valproic acid and phenytoin. It increases metabolism of other drugs via liver enzyme induction.

Lamotrigine: The enzyme-inducing drugs decrease its plasma level. Valproic acid increases its plasma level.

WOMEN AND PREGNANCY SCENARIO

Catamenial epilepsy: In women, the frequency of seizures increases during menstruation due to effects of estrogen and progesterone on neuronal excitability or change in anti-epileptic drug levels due to alteration of protein binding. Treatment options are progesterone, benzodiazepine use, increasing the dose of an anti-seizure drug or acetazolamide during luteal phase and synthetic hormones such as medroxyprogesterone (Depo-Provera) or sustained oral contraceptives to stop menses.

Pregnancy: It is useful to monitor serum anti-epileptic drug concentration in plasma during pregnancy as seizure frequency may change. Lamotrigine and levetiracetam are the safest drug for use in pregnancy. Patients should be advised to take folic acid supplements as some antiepileptics can cause lack of folic acid levels leading to neural tube defects, e.g. carbamazepine.

There are risks with other antiepileptics given during pregnancy:

Increased risk of fetal abnormalities with intake of phenytoin, e.g. facial deformity, cleft palate, cleft lip, cardiac defects, digital hypoplasia, nail hypoplasias.

Valproic acid and carbamazepine are associated with 1–2% neural tube defects.

Enzyme inducing drugs—phenytoin, phenobarbital, primidone cause deficiency of vitamin K. So, administer vitamin K (1 mg) at birth. Pregnant mothers should be administered vitamin K for last 2 weeks of pregnancy.

Breastfeeding: The mothers are given breastfeeding as there is lack of evidence of long-term harm to the infant by giving antiepileptics.

Status epilepticus: It is a medical condition consisting of a single seizure for more than 5 minutes or 2 or more more seizures within a 5-minute period with impaired consciousness in the interictal period. It is an emergency with cardiorespiratory dysfunction, hyperthermia and metabolic derangements that can lead to irreversible neuronal injury after 2 hrs. Most common causes:

- Withdrawal of anticonvulsants
- Metabolic derangement
- Toxicity due to drugs
- CNS infection—meningitis
- CNS tumors
- Resistant epilepsy
- Head injury
- **Treatment:** Lorazepam 4 mg, IV and readministered after 10 minutes as it has sustained anticonvulsant effect than diazepam.

If seizures fail to respond after 20 min of lorazepam, then fosphenytoin 100–150 mg/min, IV infusion is given under continuous ECG monitoring (propensity to cause arrythmias). Phenytoin sodium is used at the rate of 25–50 mg/min if fosphenytoin is not available.

Phenobarbitone sodium 50–100 mg/min, IV is another alternative treatment.

After 40 min of seizure onset, if the patient fails to respond to the above treatment, IV midazolam/propofol/thiopentone anesthesia is given.

If there is respiratory depression, institute intubation and ventilation. ABC–Airway, circulation, breathing, are taken care of.

Important Clinical Points to Remember

If 2 days have gone after fits—MRI recommended.

If road traffic accident or <1 day—CT scan (suspect bleeding)

Generalised tonic-clonic seizures (GTCS)—lamotrigine is first-line drug. Valproic acid is second-line drug—750–2000 mg BD.

Focal seizures—carbamazepine 150–1000 mg/day is first-line drug. Second-line drug is phenytoin (300–400 mg/day), third-line levetiracetam (100–300 mg BD).

Absence seizures—valproic acid, ethosuximide (750–1000 mg/day, BD.)

If there is first seizure in a patient, do CT, MRI, serum electrolytes, blood sugar, X-ray, ultrasound. If the area involved is temporal lobe, start antiepileptics.

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Chapter
12

Treatment of Parkinsonism

Parkinsonism is a gradually progressive neurodegenerative disorder, especially affecting middle or elderly age group, clinically presenting with four cardinal features: Akinesia/hypokinesia, muscular rigidity, resting tremors and postural abnormality. It is characterized by cogwheel rigidity—rigidity during flexion and extension throughout the movement, pill rolling tremors–resting tremors, festinating gait—patient has short and fast steps with forward flexed posture, Myerson's sign +ve on tapping the glabella (blinking of eyes due to basal ganglia involvement), Souques phenomenon when a patient seated in a chair is suddenly tilted backward, there is absence of normal reflex (leg extension) to counteract the loss of balance.

It was first described by James Parkinson in 1817 as the shaking palsy or paralysis agitans. Parkinsonism has prevalence of 1/1000 of the general population and 1% in elderly.

It is a disorder of the central nervous system that affects movement due to nerve cell damage in the brain causing accelerated loss of dopamine and dopamine receptors. It is due to degeneration of nerve cells in substantia nigra in the midbrain with eosinophilic hyaline intraneuronal inclusions called Lewy bodies. Parkinsons often starts with tremor in one hand. Other symptoms are slow movement, stiffness and loss of balance, gait disturbance (reduced swinging of arms while walking deteriorating to footdrop). Also, there are problems with cognition, behaviour, sleep and sensory systems which can progress to dementia in advanced stages. Magnetic response imaging or DaT scan are used to help in diagnosis.

The goal of medical management of Parkinsons disease is to manage symptoms and signs as long as possible while keeping side-effects minimal. The medications that increase dopamine levels in the brain are used.

ETIOLOGY

Most common cause of parkinsonism is idiopathic, where no cause is identified. Other causes are viral inflammation, head injury, stroke and poisoning by 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP).

Genetics play an important role in the etiology of this neurodegenerative disease accounting for 10% of all cases. Several genetic mutations have been found in patients and families with both autosomal dominant as well as autosomal recessive pattern of inheritance.

The process of neural injury is multifactorial and due to interaction between predisposing genetic factors, environmental factors, dietary factors, etc.

DOPAMINE BIOSYNTHESIS AND METABOLISM

Dopamine is incapable of crossing the blood–brain barrier (BBB), and it must be produced within the central nervous system (CNS) in order to act in the striatum. It is primarily synthesized in dopamine producing neurons (dopaminergic neurons) within the brain, with small amounts of dopamine also being produced in the medulla of the adrenal glands.

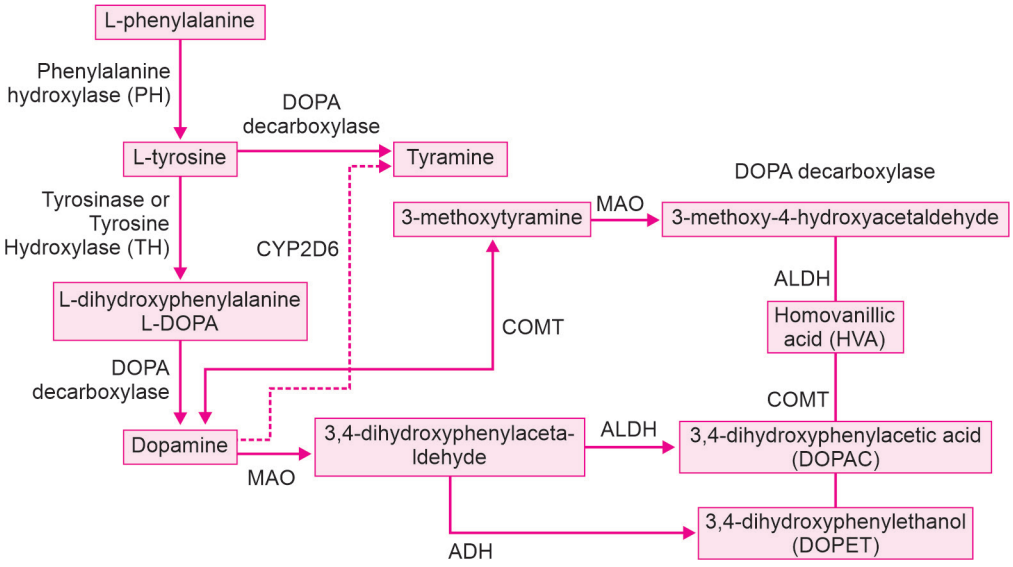

Fig. 12.1: Dopamine synthesis and metabolism

Dopamine Synthesis and Clearance Metabolic Pathway

Dopamine is synthesized from phenylalanine or tyrosine via stepwise reactions catalyzed mainly by phenylalanine hydroxylase, tyrosinase, and DOPA decarboxylase. It can also be synthesized from tyramine in a minor pathway by CYP2D6. Dopamine is effectively degraded into the main inactive metabolites DOPAC and HVA via a series of reactions-mediated predominantly by the enzymes monoamine oxidase (MAO), catechol-*O*-methyltransferase (COMT), aldehyde dehydrogenase (ALDH), and antidiuretic hormone (ADH) (Fig. 12.1).

MANAGEMENT

There is no gold standard of treatment strategy, with medication regimes targeted as individual regimen, keeping in mind the severity and temporal nature of their symptoms, as well as the side-effects that they experience. At present there is no cure for parkinsonism. Multiple components in this pathway have been targeted for the treatment of parkinsonism. The mainstay of treatment is dopamine replacement. This is achieved either directly by levodopa or indirectly with dopamine agonists or other drugs enhancing dopaminergic transmission.

Levodopa

Levodopa is precursor to dopamine and replenishes depleted dopamine in the striatum. The mainstay of current PD treatment are levodopa-based preparations, designed to replace the dopamine in the depleted striatum.

Mechanism of action: Levodopa after absorption and transit across the BBB is converted into the dopamine in the brain by DOPA decarboxylase enzyme.

Dosage: It is usually recommended for patients to be commenced on a low dose of levodopa, with the dose being titrated up based upon the patient's response to treatment, and the dose also adjusted against the adverse effects experienced. Most patients require a dose in the range of 150–1000 mg daily, divided into multiple doses.

Side-effects

- **Wearing off effect:** As parkinsonism progresses, the duration of benefit from each dose of levodopa may shorten.
- **Dyskinesias** are involuntary twisting hyperkinetic movements, which usually occur when the drug is at peak dose (but may also occur as the drug is wearing-off or even during off-periods), especially on prolonged and high dose of levodopa.

The on–off phenomenon—late deterioration in response to levodopa may occur in advanced parkinsonism after 3–5 years in some patients due to loss of capacity to store dopamine. This manifests as on-off effect due to fluctuations in response at different time of the day between mobility and immobility. This is due to variable drug absorption and transport across the blood–brain barrier (BBB) causing fluctuations in pre-synaptic and post-synaptic dopamine levels in the nigrostriatal pathway. These patents must be treated with smaller more frequent doses of levodopa 50–100 mg q2-3h or with addition of selegiline 10 mg/day to prolong and potentiate levodopa doses.

Other important side-effects are gastrointestinal disturbances such as nausea and vomiting, ortho static hypotension, neuropsychiatric features including anxiety and hallucinations, arrythmias.

Some strategies used to tideover the adverse effects of levodopa include using the lowest effective dose, fractioning of the dose, and the use of alternative treatments. Levodopa is administered in combination with DOPA decarboxylase inhibitors such as benserazide and carbidopa. These compounds do not cross the BBB, but selectively prevent the peripheral conversion of levodopa to dopamine, thereby reducing its peripheral side-effects. The most frequently prescribed combination drugs are carbidopa/levodopa and benserazide/levodopa. 25 mg carbidopa or benserazide per 100 g of levodopa is administered in 3 equally divided doses. Levodopa should be administered at least 30 minutes before meals.

Drug Interactions

Pyridoxine should be avoided with levodopa as it enhances peripheral conversion of levodopa to dopamine.

Central dopamine antagonists such as antipsychotics, e.g. phenothiazines, neuroleptics—chlorpromazine, antiemetic—metoclopramide antagonize the therapeutic effect of levodopa by blocking DA receptors in the corpus striatum and lead to drug-induced parkinsonism. Cholinergic syndromes are more common—increased salivation, problem in speaking, mood changes, loss of interest in life, mask like-face, etc.

Non-selective MAO inhibitors: Severe hypertension may be produced due to inhibition of breakdown of peripherally formed DA and NA from levodopa.

Dopamine Agonists

Dopamine agonists are categorized into ergot derivative (bromocriptine, pergolide, cabergoline, lisuride) and non-ergot derivative (pramipexole, ropinirole, rotigotine, apomorphine), based on receptor specificities. They provide a means of directly stimulating dopamine receptors and are less effective than levodopa. They are used in early disease to delay initiation of levodopa therapy. When used as adjunctive to levodopa in advanced stages, they cause clinical improvement and reduced levodopa dosage.

Bromocriptine is an agonist at D2 receptors and a partial D1 antagonist, also has weak α-adrenergic blocking activity. Its half-life is 3 hrs. The dose is 1.25 mg, BD after meals.

Pergolide is an agonist at both D1 and D2 receptor subtypes.

Ropinerole and **pramipexole** are selective agonists at D2 receptor sites.

Ropinerole: 9–16 mg (maximum 24 mg) total daily dose, divided into three to four doses.

Rotigotine: Rotigotine patch (4–6 mg) for those unable to take orally, for example, when they are kept nil-by-mouth in preparation for surgery.

Pramipexole: 0.125 mg, TDS, initially, doubled every week with total dose is 1.5–2.4 mg/day.

Treatment with dopamine agonists has shown results in a reduced incidence and severity of dystonia, motor fluctuations, and dyskinesia in comparison to levodopa. However, they may cause other severe adverse effects like postural hypotension, somnolence, nausea, fatigue with bromocriptine and pergolide. Because pramipexole and ropinirole are better tolerated drugs, they are increasingly used as monotherapy.

Inhibitors of Monoamine Oxidase B (MAO-B)

MAO-B is one of the main enzymes involved in the breakdown of dopamine. Reducing the activity of this enzyme therefore results in increased dopaminergic activity within the striatum, mediated by endogenous dopamine.

MAO-B inhibitors use relieves motor symptoms. It delays the need for levodopa therapy in patients with early Parkinsons disease. MAO-B inhibitors may also be used in combination with levodopa-based preparations, to allow for a reduction in the levodopa dose. Selegiline may slow progression of disease by reducing formation of free radicals produced during metabolism of dopamine.

Commonly used MAO-B inhibitors include selegiline and rasagiline. The recommended dosage for selegiline is 5–10 mg daily, and for rasagiline it is 0.5–1 mg once daily.

Side-effects: The adverse effects include insomnia, anxiety, postural hypotension.

Selegiline should not be coadministered with tricyclic antidepressants or selective serotonin uptake inhibitors cause hypertensive crisis with pethidine. It can cause adverse drug reactions like hyperpyrexia, agitation, delirium and coma.

Catechol-O-methyl Transferase (COMT) Inhibitors

COMT metabolizes dopamine and levodopa. COMT is present in periphery as well as in CNS and its inhibition prolongs the brain concentration of levodopa. COMT inhibitors are predominantly used as adjunctive therapy to levodopa, prolonging its duration of action

by increasing its half-life and its delivery to the brain. They are used in patients with motor fluctuations as they increase the on time.

COMT inhibitors—entacapone, tolcapone—are used in a combination preparation along with carbidopa and levodopa. The typical dosage for entacapone is 200 mg four to eight times a day with each levodopa dose and 100 mg three times a day in the case of tolcapone.

Side-effects: COMT inhibitors can lead to the amplification of levodopa-induced side-effects, including dyskinesias, and it may be that they necessitate a reduction in the levodopa dose. Tolcapone is associated with fatal hepatotoxicity and requires monitoring of liver enzymes.

Anticholinergics

The blockade of dopamine receptors by antipsychotics leads to increased cholinergic activity of striatal neurons. The effect of anticholinergics in parkinsonism is by acting as antagonists at cholinergic receptors in the striatum, reducing the activity of the neurotransmitter acetylcholine.

The main role of these drugs is in young patients at early stages of the disease for the relief of mild movement symptoms particularly tremors and muscle stiffness. They exert modest antiparkinsonian actions. Anticholinergics include benztropine, 1–4 mg BD, orphenadrine 150–400 mg/day, procyclidine 5–30 mg/day, and trihexyphenidyl 4–12 mg/day, biperiden–2–12 mg/day, oral, IM, IV.

Side-effects: The common adverse effects include blurred vision, dry mouth, constipation, drowsiness, trouble in urinating, urinary retention, confusion, cognitive impairment, hallucinations, dizziness, trouble swallowing, dyskinetic movements, and memory problems. Avoid in elderly patients or those with cognitive problems.

Antihistaminics: Having central anticholinergic action can be used for treatment of drug induced PD, e.g. diphenhydramines, promethazine but cause marked sedation. They can be used in elderly who may not be able to tolerate the most potent anticholinergics.

Amantadine Causes Release of DA and Blockade of Reputake of DA

It is used in early stage of parkinsonism and as adjunct to levodopa therapy. It may also allow for a lower dose of levodopa to be used, reducing the risk of levodopa-induced dyskinesias due to blockade of N-methyl-D-aspartate (NMDA) glutamate receptors. It is modestly effective in treating symptoms of parkinsonism.

Side-effects are hallucinations, confusion and impaired concentration, livedo reticularis, leg swelling, blurred vision, nausea and vomiting, appetite loss, insomnia and nightmares, sweating, agitation, and headache. The dose is 100 mg BD.

Non-pharmacological approaches: Brain stimulation by high frequency electrical stimulation of the thalamus, subthalamic nucleus, or globus pallidus can improve various symptoms of parkinsonism and reduce levodopa dose.

Levodopa + β-blocker [if pulse rate (PR) >90]. The dose of levodopa is 100–200 mg (maximum 800 mg)

Juvenile parkinsonism— <30 years–mentally retarded with same features.

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Chapter
13

Treatment of Psychotic and Mood Disorders

Psychotic illness and mood disorders include schizophrenia, depression, and mania and anxiety disorders. Antipsychotic drugs are used in these illnesses along with psychotherapy being adjunctive.

SCHIZOPHRENIA

The most common primary psychosis is schizophrenia. It has onset in late adolescence or early adulthood. Its worldwide prevalence is 0.4%. Schizophrenia patients have marked distortions in thinking and perception and inappropriate emotions. A normal feeling of individuality, uniqueness and self-direction is lost. Behavior is seriously affected leading to adverse social consequences. Delusions (strong belief in ideas that are false and without any basis in reality), and hallucinations (commonly auditory hallucinations, e.g. hearing voices) are characteristic of this disorder. Individuals with schizophrenia have good orientation to person, place and time.

The exact cause of the schizophrenia is unknown. The key defect is increased dopamine activity due to rise in number of brain dopamine (DA) D2 receptors or excess availability of DA from D2 receptor activation.

Diagnosis

Primarily based on clinical presence of emotional blunting, poor socialization, and cognitive defect. Positive symptoms are characterized by delusions and hallucinations. Negative symptoms include a flattened effect and emotional and social withdrawal.

Management

Its management includes psychosocial intervention and antipsychotics drugs. The antipsychotic drugs target at basically the most serious symptoms, including hallucinations, delusions, agitation and disorganised thought and behaviour. Antipsychotic medications work by altering the balance of certain neurotransmitters, primarily by blocking postsynaptic D2 receptors in CNS. They are classified into conventional or first-generation antipsychotics and atypical or second-generation antipsychotics.

First generation antipsychotics are further classified into **phenothiazines** (chlorpromazine, levomepromazine, promazine, pipotiazine, pericyazine, perphenazine, fluphenazine prochlorperazine and trifluprom azine), **butyrophenones** (benperidol and haloperidol), **diphenylbutylpiperidines** (pimozide), **thioxanthenes** (flupenthixol and zuclopenthixol) and the **substituted benzamides** (sulpiride).

Second generation antipsychotics (atypical) include amisulpiride, aripiprazole, clozapine, olanzapine, sertindole, ziprasidone, risperidone, quetiapine and zotepine.

Most common drugs used for schizophrenia are chlorpromazine, fluphenazine, haloperidol, risperidone, clozapine, olanzapine, and quetiapine. First- and second-generation antipsychotics are similarly effective in the acute treatment of schizophrenia. Clozapine is an exception which is more effective than first generation antipsychotics in the pharmacological treatment of refractory schizophrenia. After 6–8 weeks, effectiveness of treatment should be assessed and after the resolution of acute episode, generally prolonged treatment for at least one year should be provided (Table 13.1).

Table 13.1: Doses of antipsychotics and side-effects

Antipsychotics	*Adult dose range (mg/day)*		*Side-effects*
	Acute	*Maintenance*	
Chlorpromazine	100–1600 mg, oral; 25–400 mg, IM	50–40 mg, oral	Sedation, postural hypotension
Trifluoperazine	4–40 mg, oral	5–20 mg, oral	Sedation, extrapyramidal side effect
Fluphenazine	12.5–50 mg, IM (deaconate, fortnightly)		
Haloperidol	5–20 mg, oral 5–20 mg, IM	1–5 mg, oral 25–200 mg, IM, monthly)	Sedation, extrapyramidal side-effects, dystonia, akathisia, amenorrhea
Risperidone	4–6 mg, oral		Sedation, extrapyramidal side effects, amenorrhea
Olanzapine	7.5–30 mg, oral		Sedation, postural hypotension, weight gain
Quetiapine	300–800 mg, oral		Sedation, postural hypotension, dizziness

Antipsychotic side-effects are generally neurologic and anticholinergic manifestations. Neurologic side-effects include parkinsonian effects (resting tremor, akinesia, rigidity), akathisia (subjective feeling of agitation) acute dystonias (slow, prolonged muscular spasms), neuroleptic malignant syndrome (fever, sweating, confusion, increased blood pressure and pulse, muscular rigidity, very high creatine phosphokinase, renal failure), tardive dyskinesia (abnormal involuntary movements of tongue, head, face, mouth), and convulsions. Anticholinergic side-effects are peripheral effects (dry mouth, blurred vision, constipation, urinary retention) and central effects (severe agitation and confusion). Other side-effects associated with antipsychotic use are sedation, weight gain, orthostatic hypotension, abnormal electrocardiogram, gynecomastia, galactorrhea, amenorrhea, impotence, leukopenia, agranulocytosis, jaundice, elevated liver enzymes, photosensitivity, skin eruptions, retinal pigmentation.

All atypical antipsychotics also block the 5HT2 receptors apart from D2 receptors. The advantages are relief of negative symptoms, resistant cases also respond. There are less chances of extrapyramidal symptoms, lesser autonomic side-effects, less hyperprolactinemia (except risperidone and paliperidone). They are effective against levodopa-induced psychosis in

patients with PD. Disadvantages are weight gain, seizures (clozapine), hypotensive (postural), hyperlipidemia and hyperglycemia (clozapine and olanzapine) and agranulocytosis (only with clozapine).

DEPRESSION

Depression is marked by depressed mood episodes. Each episode involves lowering of mood, reduction of energy, and decrease in activity. The ability to enjoy, take interest in life and concentration is reduced, and marked fatigue after minimum exertion is common. Patient complaints of insomnia and decreased appetite. Self-esteem and self-confidence are lowered and feelings of guilt or worthlessness are often present.

Depression is usually classified into mild, moderate and severe grades. Mild-to-moderate depression has depressive symptoms with some functional impairment; severe depression is marked by depressive symptoms, functional impairment, agitation or psychomotor retardation, and characteristic somatic complaints.

Antidepressants are classified based on the mechanism of action: **Tricyclic or related antidepressants** (amitriptyline, desipramine, imipramine, clomipramine, dothiepin, dosulepine, doxepin, lofepramine, nortriptyline, trimipramine, mianserine, and trazodone); **monoamine oxidase inhibitors** (moclobemide, phenelzine, isocarboxazid, and tranylcypromine); **selective serotonin reuptake inhibitors** (SSRIs) (citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, paroxetine); **other antidepressants** (duloxetine, venlafaxine mirtazapine, reboxetine).

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are used most commonly for treatment of major depression. Side-effects with tricyclics are sedation, anticholinergic effects (dry mouth, blurred vision, urinary retention, constipation, agitation, confusion), cardiovascular effects (orthostatic hypotension, tachycardia, arrhythmias), narrow angle glaucoma, prostatism and weight gain.

Amitriptyline: The starting dose is 50 mg at night, increasing 100–150 by 4–6 weeks, and if there is no response or partial, increase further to a maximum 200 mg. In elderly patients, start low with 25 mg as the starting dose, wait slowly up to 12 weeks with maximum dosage of 100 mg. TCA is contraindicated in adolescents, at risk of serious cardiac arrhythmias or with recent myocardial infarction. It is mandatory to monitor blood pressure of all cardiovascular patients on TCA.

MAO inhibitors—MAO inhibitors were used for atypical depression in which there are symptoms like oversleeping, anxiety, panic attacks, and phobias. They increase the availability of NA and Seratonin by destruction of Monoamine enzyme in the presynaptic terminal. The older MAO inhibitors—phenelzine, tranylcypromine, isocarboxazid bind irreversibly to monoamine oxidase enzyme by forming strong covalent bonds. These are called hit and run drugs. MAO inhibitors are subject to tyramine ingested in food. Their side-effects are similar to other antidepressants. MAO inhibitors also react with certain foods, beverages, medications and cause cheese reaction—characterized by severe high blood pressure, headache, rapid heartbeat, confusion, seizures, stroke and coma.

SSRIs: All of these newer antidepressants seem to have less bothersome side-effects than older TCAs, like do not cause significant CVS and anticholinergic side-effects. Most of them are given in morning, once daily dose. SSRIs have side-effects like agitation, tremor, dizziness,

headache, insomnia, nausea, diarrhoea, sexual problems, hyponatraemia, weight loss and rash. When MAO inhibitors are used with seratonergic drugs, raising the concentration of serotonin in the CNS, they cause serotonin syndrome characterized by akathisia like restlessness, muscle twitching, myoclonus, hyperreflexia, sweating, hyperthermia, shivering, tremor, erection of penis and seizures and coma in severe cases. The treatment is with BZPs, intermittent positive pressure respiration (IPPR), and cyproheptadine.

- *Fluoxetine* (longest-acting SSRI): Treatment is started with 20 mg, OD. If patient does not respond in 4–6 weeks or there is partial response, increase dose by 20 mg (maximum dose 60 mg). Pediatric and elderly patients should start with 10 mg and the dose increased gradually to 20 mg after waiting for 6–12 weeks before uptitration. Also the idea of suicide in adolescent population is monitored.
- *Sertraline* produces significant antidepressant effect in children and suitable in elderly as its elimination is not affected by aging. Dose—50, 100 mg tabs.
- *Escitalopram* can be used in patients with suicidal tendency, more potent and safer than citalopram. Dose: 5, 10 mg tabs.

Selective seratonin norepinephrine reuptake inhibitors (SNRIs): *Venlaflaxine* blocks the reuptake of NA, 5HT and dopamine. However, it causes severe nausea and persistent rise in BP at daily dose more than 200 mg. Dose—25, 37.5, 75 mg tabs.

Duloxetine: It significantly metabolized in liver and antidepressant action is similar to TCA. It is also effective in chronic pain like diabetic neuropathy, peripheral neuropathy, generalized anxiety disorder, fibromyalgia and stress urinary incontinence in women. Dose—20, 30, 60 mg tabs.

BIPOLAR AFFECTIVE DISORDER

Bipolar affective disorder or manic-depressive illness is a mental illness characterized by episodes of both mania and major depression alternating episodes. In patients with severe manic episodes, antimaniac drugs are rapidly effective to control mania. Antimanic drugs are lithium, valproic acid, lamotrigine, calcium channel blockers, carbamazepine.

Lithium—is the preferred treatment of bipolar disorder in maniac phase. Dopamine and glutamate neurotransmitters are reduced but inhibitory (GABA) neurotransmitters are increased. When Mania is mild, Li alone may be an effective treatment, starting dose 600–1200 mg. Regular serum level monitoring to maintain therapeutic levels 0.8–1.0 mEq/litre is essential. It is crucial to monitor TSH and S. creatinine levels also. Its side-effects are tremors, sedation, weight gain, polyuria, polydipsia, impaired coordination, cognitive problems, cardiac arrhythmias, hypothyroidism, diabetes insipidus

Valproic acid—first-line treatment of mania, has been effective in patients who have failed to respond to lithium. The starting dose is 500 mg/day increase up to 2000 mg. Valproate causes gastrointestinal pain, benign hepatic transaminase elevations, tremor and sedation. Patients with hepatitis have propensity for hepatotoxicity. Less frequent are reversible, mild, asymptomatic leucopenia and thrombocytopenia. Rare fatal adverse effects are haemorrhagic pancreatitis and agranulocytosis.

Carbamazepine—may be used to treat acute mania, bipolar disorder. Start with 200 mg twice daily to max 600 mg/day, increased as needed. Side-effects can be drowsiness, ataxia, diplopia, nausea, diplopia. Rash, mild leucopenia, mild liver enzyme elevations, mild

thrombocytopenia, hyponatremia and hypoosmolality are less frequent. Rare and fatal side-effects include agranulocytosis, aplastic anemia, thrombocytopenia, hepatic failure, Stevens–Johnson syndrome, toxic epidermolysis and pancreatitis. Monitor blood and hepatic parameters.

Lamotrigine—inhibits neuronal sodium channels and prevents release of excitatory aminoacids—glutamate and aspartate.

Calcium channel blockers: Who fail to other drugs, verapamil should be used till delivery in pregnant.

Atypical antipsychotics: Adding a benzodiazepine—clonazepam/lorazepam or as monotherapy—olanzapine, risperidone, aripiprazole, quetiapine, are now first-line drugs for acute mania. Older antipsychotics are most effective in cases requiring urgent parenteral therapy. An atypical antipsychotic is combined with valproate or lithium and found highly efficacious in acute and also maintenance therapy of bipolar disorder.

ANXIETY

It is an emotional disorder marked by uneasiness, discomfort and concern of fear. A restless state of mind is created without interfering with normal mental or physical actions. Anxiety is characterised by physiologic manifestations like sweating, tremors, dizziness, palpitations, mydriasis, tachycardia, gastrointestinal disturbances, diarrhoea, and urinary urgency and frequency. Antianxiety drugs include **benzodiazepines, β-blockers, zolpidem and zaleplon**.

Benzodiazepines are given at low doses. Benzodiazepines are prescribed to treat anxiety or insomnia that is severe, disabling and causing extreme distress. Benzodiazepines are classified based on their elimination half-life, into short, intermediate and long half-life agents. Short/intermediate half-life agents include alprazolam (intermediate), lorazepam (short), oxazepam (short), temazepam (intermediate) and triazolam (ultra-short); long half-life agents include diazepam, chlordiazepoxide, flurazepam and nitrazepam.

β **blockers**–treat palpitation, rise in BP, shaking, tremor, GIT hurrying due to sympathetic overactivity in anxiety disorder. They do not affect psychological symptoms but are valuable in acute stressful situations.

Zolpidem and zaleplon: Non-benzodiazepine hypnotics such as zopiclone and zolpidem are used in insomnia. However, these agents cause rebound symptoms, dependence and other adverse reactions. They bind to BZP receptors and facilitate GABA-mediated inhibition. Zolpidem has a rapid onset and short duration of action. Its side-effects are drowsiness, dizziness, and diarrhea. Zolpidem increases the depressant effects of other sedatives.

Azapirones: Buspirine, Gepirone, Ipsapirone act as 5HT partial agonist and reduce the 5HT level in the limbic system and thus relieve anxiety. The anxiolytic effect occurs after 1–2 weeks, without causing sedation.

Buspirone: First agent of this class to be used clinically. It does not potentiate other CNS depressants and does not affect psychomotor and driving skills, maintaining alertness. The dose is 5–15 mg OD up to three times a day.

Treatment of anxiety—is started only if frequent anxiety symptoms are present and are in severe form leading to distress and impaired performance. Short-term treatment with benzodiazepines (BZDs) should be started. BZDs should be withdrawn after initial

2–4 weeks. BZDs should be tapered gradually. If anxiety is refractory to BDZs, then long-term treatment with antidepressants preferably with selective serotonin reuptake inhibitors (SSRIs) is given followed by tricyclic antidepressants and MAO inhibitors. Patients with peptic ulcer, hypertension, ulcerative colitis, GIT reflux, thyrotoxicosis, angina, peptic ulcer are given low doses of BZD in addition to specific therapy (Table 13.2).

Table 13.2: Drugs used in anxiety with doses and adverse effects

Group of drug	*Dosages (mg/day)*	*Adverse effects*
Benzodiazepines		On long-term use: Tolerance, dependence and withdrawal, dizziness,ataxia, daytime drowsiness, amnesia, in overdose respiratory depression
Clonazepam	0.5–2	
Alprazolam	0.5–4	
Lorazepam	1–4	
Diazepam	5–15	
Selective serotonin reuptake inhibitors		Gastrointestinal side-effects, sleep disturbance, headache, anxiety, prolonged bleeding time, hyponatremia, sexual dysfunction, discontinuation syndrome
Sertraline	50–200	
Escitalopram	10–20	
Citalopram	20–40	
Paroxetine	20–50	
Fluoxetine	20–60	
Fluvoxamine	100–300	
Tricyclic antidepressants		Sedation, hypotension, cardiac side-effects mainly prolonged QT interval, anticholinergic effects, weight gain
Imipramine	75–300	
Clomipramine	75–300	
Amitriptyline	75–200	
Beta-blockers		Bradycardia, hypotension, worsening of asthma and hypoglycaemia, GI side-effects
Propranolol	10–20 mg bid or tds	

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Chapter 14

Treatment of Acute and Chronic Pain and Treatment of Migraine

INTRODUCTION

Pain is not just a sensory modality but an experience. According to the International Association for Study of Pain: Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. The term unpleasant comprises the whole range of disagreeable feelings from being inconvenienced to anguish, anxiety, depression and desperation to the ultimate cure as suicide. It is a subjective perception which involves complex interactions between sensory, psychological, cultural and environmental factors as well as previous experience of pain. Pain can basically be of 2 types—nociceptive pain and neuropathic pain.

It is the most common symptom that brings the patient to a physician and hence its management is a vital component of patient care, especially in emergency setup where it can hinder treatment. The term nociception is derived from *noci* (Latin for harm or injury) and is used to describe neural responses to traumatic or noxious stimuli. Pain can be classified as acute or chronic, or in broad categories based on the origin of the injury to pain fibers. Somatic pain has nociceptors that originate in the peripheral tissues such as skin and muscle and allow more specific ability to localize the source. Visceral pain originates in internal organs. These nociceptors are activated by actual tissue damage, or in the absence of damage, pressure and stretch of the organ. Visceral pain is not well-localized and frequently the pain is referred to another area of the body. This is due to somatic fibers in a separate anatomic location intermingling with visceral fibers within the dorsal column and stimulating the somatic fibers, thus causing pain to be felt in the undamaged somatic region.

ACUTE PAIN

Acute pain is the most frequently encountered variety of pain all over the world. It is an important aspect of childbirth, surgeries, trauma and acute medical illness. Acute pain is also responsible for being the reason in more than two-thirds of consultations in emergency department.

Pain is felt by naked nerve endings called nociceptors found in almost every tissue in millions—probably about 1300/square inch of skin. Uncontrolled and unrelieved acute pain not only results in high degree of suffering and discomfort, but also results in terrible consequences like delayed wound healing, loss of body weight, increased hospital stay, and risk of development of chronic persistent postsurgical pain. Pain is initiated when

specialized nerves, called nociceptors, are activated in response to adverse chemical, thermal or mechanical stimulus. Activation can be direct due to trauma or indirect via biochemical mediators released from damaged tissues and circulation. These mediators can further augment the pain process by up-regulating pain receptors and recruiting additional surrounding nociceptors into activity. Mediators include, but are not limited to, prostaglandins, bradykinins, histamine, serotonin and arachidonic acid. The severity of the pain sensed is dependent on the number of receptors stimulated, the duration of the stimulus and the amount of mediators released locally. Once the nociceptor is depolarized, a signal is sent from the periphery into the dorsal horn of the spinal cord, where pain signals are integrated to elicit spinal reflexes such as withdrawal of the affected area, muscle spasms, and to release additional mediators within adjacent spinal segments and relay information to higher cortical areas (Fig. 14.1).

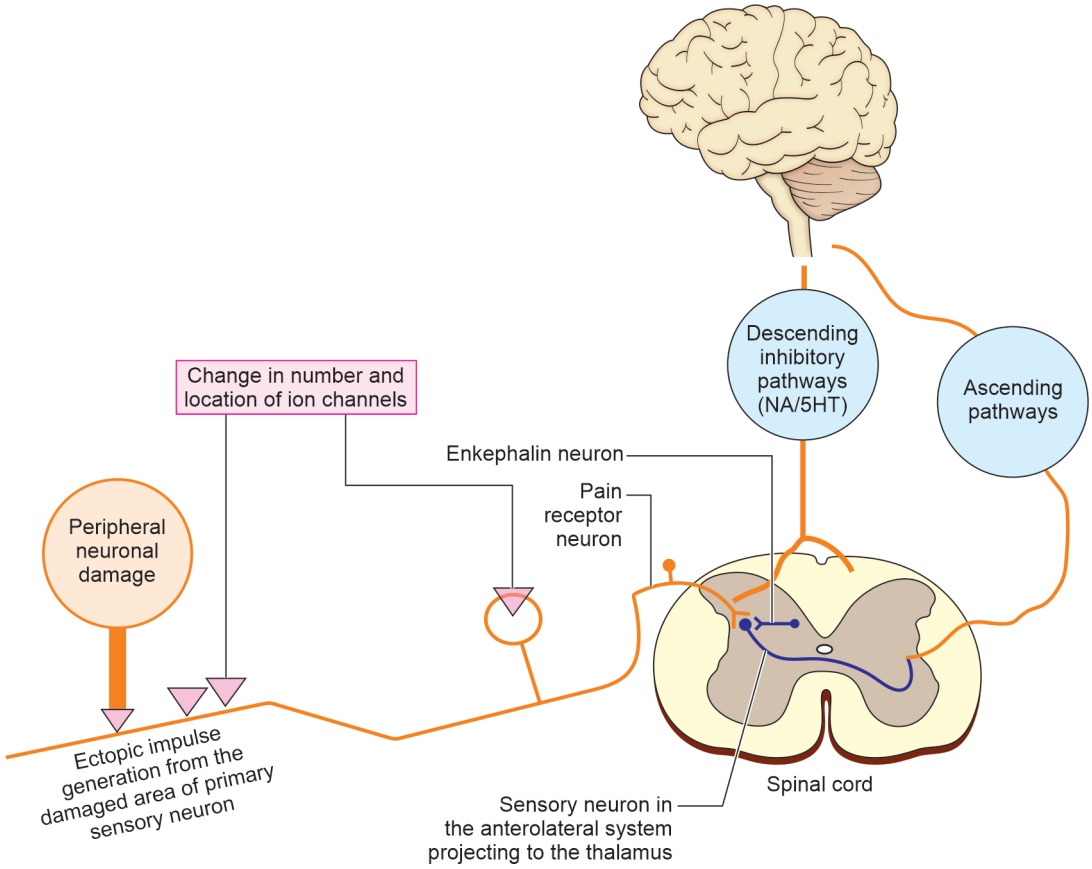

Descending inhibitory pathways (NA/5HT)
Ascending pathways
Change in number and location of ion channels
Enkephalin neuron
Pain receptor neuron
Peripheral neuronal damage
Ectopic impulse generation from the damaged area of primary sensory neuron
Spinal cord
Sensory neuron in the anterolateral system projecting to the thalamus

Fig. 14.1: Pain transmission pathway

Pain fibres are divided into two major groups based on presence or absence of myelination. Myelinated A-delta fibers transmit the signal rapidly and are responsible for the initial sharp pain changing later to burning or soreness. Unmyelinated C fibers are relatively slower in speed and are associated with deep aching or throbbing types of pain that follows the initial sharp pain. Both types of pain fibers then cross the midline and stimulate the ascending pain

fibers in the spinothalamic tract. Substance P is one of the key neurotransmitters relaying the pain signal from the periphery and the spinothalamic tract. Fibers in the spinothalamic tract terminate in the thalamus, limbus and brain stem. Further information is transmitted to multiple cortical areas of the brain responsible for localization and pain perception. Descending pain fibers are, in turn, activated from the cerebral cortex via efferent pathway to the spinal cord and periphery and act to decrease the intensity of the pain signal via encephalin, serotonin and gamma-aminobutyric acid (GABA) neurotransmitters.

In addition to pain perception, activation of the pain pathway causes the release of hormones and vasoactive substances such as cortisol, vasopressin, and catecholamines. The release of these factors, referred to as the surgical stress response, peaks in the initial hours of the post-operative period. The stress response can cause hyperglycemia and impairment of immunological functions, as well as breakdown of fat and muscle. Tissue trauma also causes release of vasoactive mediators which play a role in pain. Mast cells, platelets and plasma components contribute histamine, leukotrienes, and bradykinins. Independently, the mediators further sensitize nociceptors, and activate additional cytokines that augment inflammation already present.The autonomic nervous system can also be activated by pain. This occurs in large measure in the dorsal horn, and is responsible for the associated symptoms seen with pain such as nausea, sweating, alteration of heart rate and blood pressure. An excellent example of autonomic activation associated with pain is angina, where myocardial pain is expressed with symptoms of nausea, sweating, in addition to chest pressure.

PRINCIPLES OF ACUTE PAIN MANAGEMENT

The underlying causes of acute pain should always be treated first (where possible). The primary aim of acute pain management is to provide treatment that reduces a patient's pain with minimal adverse effects while allowing them to maintain function. The secondary aim is to prevent the chronification of pain. Assessment methods should be relevant to the individual patient; selection of a pain measurement tool should take into account any relevant developmental, cognitive, emotional, language and cultural factors.

The effective management of acute pain is important from the human perspective for:

a. Providing relief from suffering;
b. Decreasing incidence of negative consequences, including the risk of pain chronification, delayed recovery (with an associated increased risk of infection), impaired sleep, reduced mobility and poorer quality of life.
c. Preventing other potential outcomes of delayed or ineffective analgesia including impaired immunity, increased hospital re-admission rates, psychological impacts such as post-traumatic stress disorder, tachycardia, hypertension, increased myocardial oxygen demand, hyperglycaemia, insulin resistance, changes in fat and protein metabolism, and coagulopathies.

Figure 14.2, the WHO pain relief ladder provides a stepped approach to the management of cancer pain in which, if pain occurs, there should be prompt oral administration of drugs until the patient is free of pain.

To maintain freedom from pain, drugs should be given at regular intervals in accordance with their pharmacological characteristics—a 'by the clock', rather than an 'on demand as pain arises' administration. A number of modifications have been proposed to adapt

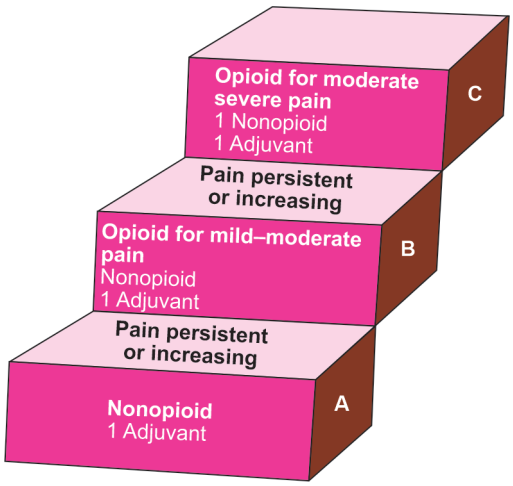


Fig. 14.2: WHO pain relief ladder

the ladder to different types of pain, such as acute pain, and to take into account recent developments in analgesia such as nerve block techniques and sublingual and transdermal opioids.

ASSESSMENT OF PAIN

As pain is a subjective experience which is influenced by psychological, social, cultural and other variables, therefore, reliable and accurate assessment of pain severity is a challenge. Reassessment of pain is as important as the initial assessment, and should take place at a frequency guided by the patient's pain severity. Patients in the emergency department prefer pain assessment to take place approximately every 15 minutes, with more frequent assessments when pain is severe. An effective patient history is invaluable and marks the first step in pain assessment and management. A careful documentation of clinical symptoms and thorough physical examination will lead to appropriate differential diagnosis and management plan. The clinician should focus on: Location of pain; temporal characteristics; aggravating and alleviating factors; impact of pain on function and quality of life; past treatment and reports; and also patient's expectations and goals for their pain.

The numerical rating scale, Wong-Baker FACES rating scale, visual analogue scale (VAS), McGill Pain Questionnaire (MPQ) are some of the commonly used scales. In numerical scale (delivered verbally or in a written format), 0 corresponds to no pain and 10 reflects the worst possible pain (Fig. 14.3). Mild pain would be considered as a pain score of 1–3, moderate pain a score of 4–7 and severe pain a score of >7.

The visual analogue scale (VAS) is the most commonly used scale for rating pain intensity in clinical trials. It takes the form of a 100 mm/10 cm horizontal line, the left end of which is defined as 'no pain' and the right end as 'worst possible pain', with no other tick marks along the length of the line.The patient marks the point along the line that they feel corresponds to the level of pain that they are experiencing, and the pain score is recorded as the measurement in millimeters or centimeters from the left end of the scale to the patient's mark. A reduction in pain intensity of 30–35% on the VAS has been rated as clinically meaningful by patients with acute pain in the emergency department (ED).

The functional activity scale (FAS) is a simple 3-level categorical score used to assess whether a patient can undertake appropriate activity at his current pain level and trigger retreatment if activity is curtailed by pain. The patient is asked to complete a particular activity or is assisted in doing so, and their ability to do so is assessed as A (no limitation due to pain), B (mild limitation, with the patient able to complete the activity but experiencing moderate-to-severe pain in the process) or C (significant limitation, where the patient is unable to complete the activity due to pain). The patient's FAS score can then be used to assess the effectiveness of pain treatment on function.

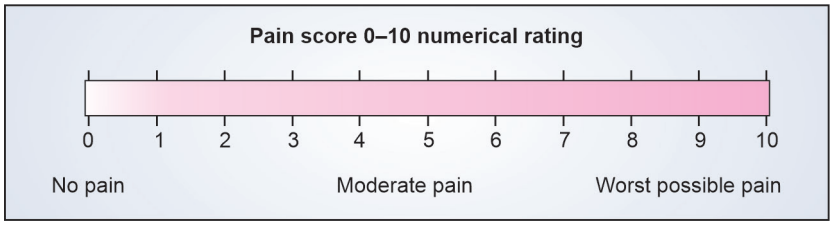


Fig. 14.3: Numerical rating scale

However, this scale has not yet been independently validated. Special consideration must be given to the assessment of acute pain in babies and young children, the elderly (particularly those with dementia) and unconscious or sedated patients.

Scales for the assessment of the intensity of acute pain in neonates include the premature infant pain profile (PIPP), the CRIES (C-Crying; R-requires increased oxygen administrations; I-increased vital signs; E-expression; S-Sleeplessness) the neonatal facial coding scale (NFCS). These scales rely on observations of variables such as the presence or absence of crying, facial expression, heart rate and other vital signs.

The face, leg, activity, cry and consolability (FLACC) scale can be used to assess pain in children between the ages of 2 months and 7 years, in children with cognitive impairment, or in individuals of any age that are unable to communicate their pain. The FLACC scale has 5 criteria (facial expression, position/movement of legs, overall activity, presence/degree of crying, and ability to be consoled or comforted) which are each assigned a score of 0, 1 or 2, giving a total score in the range of 0–10, with 0 representing no pain. A modified version of the FLACC scale, FLACC-R has been developed for children with cognitive impairment.

The Wong-Baker FACES rating scale, is designed for children 3 years of age and older, is useful for patients with whom communication may be difficult. Patients are shown a range of faces showing varying degrees of distress, and asked to select the expression that corresponds to the amount of pain that they are currently experiencing (Fig. 14.4).

Pain is generally underreported in the elderly, even those with normal cognition. Untreated pain in the elderly leads to increased disability and decreased quality of life. Verbal descriptor scales have been shown to be most sensitive and reliable in older adults, including those with mild-to-moderate cognitive impairment. The pain assessment in advanced dementia (PAINAD) scale is an observer-rated tool for assessing pain related behavior, and is partly based on the FLACC scale. It consists of five items: Breathing, negative vocalisation, facial expressions, body language and consolability. Each item can be rated from 0 to 2, to generate a score ranging from 0 to 10. The behavioral pain scale (BPS) has been validated for use in critically ill, sedated and mechanically ventilated patients (Table 14.1). The BPS score is calculated as the sum of three subscales (facial expression, upper limb movements and

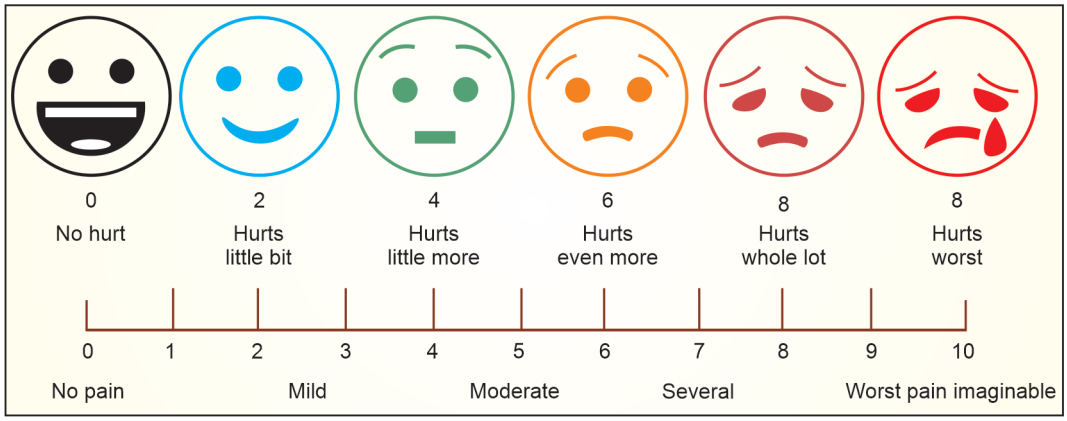


Fig. 14.4: Wong-Baker FACES rating scale

compliance with mechanical ventilation), each with a score ranging from 1 to 4 of the pain scales developed for use in adult patients under intensive care. The BPS is considered to be one of the most valid and reliable.

Table 14.1: The behavioural pain scale (BPS)

Sub-scale	*Description*	*Score*
	Relaxed Partially tightened	1 2
Facial expression	Fully tightened Grimacing No movement	3 4 1
Upper limbs	Partially bent Fully bent with finger flexion Permanently retracted Tolerating movement	2 3 4 1
Compliance with ventilation	Coughing but to lerating ventilation for most of the time Fighting ventilator Unable to control ventilation	2 3 4

NON-PHARMACOLOGICAL THERAPIES IN ACUTE PAIN

The relaxation training by focusing on breathing patterns, concentrating on mental imagery of relaxing scenes and gradually releasing of muscle tension throughout the body; can help patients to reduce stress and tension. Music often forms an important part of the relaxation process. As relaxation techniques generally require practice on the part of the patient, so they have limited immediate use in an emergency situation but may be valuable later when the patient is recovering.

Hypnosis

Hypnosis has a long history of use in acute pain conditions. In 12 of 19 studies reviewed, hypnosis was more effective in reducing pain scores than the comparator treatments which included no treatment, standard care or other psychological interventions.

Attention Control Methods

Attention-based techniques to control pain include distraction techniques, concentration on imagined scenes or sensations, focus on external stimuli such as music or odours, or techniques to change the patient's emotional state to a more peaceful and comfortable one. Attention control techniques including the use of imagery, music and jaw relaxation have demonstrated benefits in acute postoperative pain in a number of older studies. In older children, distraction may be possible through coaching or coping statements, watching video, playing video games or virtual reality.

Cognitive Behavioural Intervention

Cognitive behavioural therapy (CBT) is a psychological technique that includes cognitive and behavioural modifications of specific activities to reduce the impact of pain and disability and overcome barriers to physical and psychosocial recovery. The use of CBT to address acute pain has little evidence in a pre-hospital or ED setting.

Transcutaneous Electrical Nerve Stimulation (TENS)

Transcutaneous electrical nerve stimulation (TENS) is a treatment that relieves pain by administering pulsed electrical currents across the intact surface of the skin to selectively stimulate non-noxious, low-threshold afferent peripheral nerve fibres in the skin. This is claimed to inhibit transmission of nociceptive information at the level of the spinal cord. High-intensity TENS can significantly reduce requirements for postoperative analgesia. TENS also resulted in reduced patient anxiety.

Acupuncture and Related Techniques

Acupuncture is a well-known traditional therapy that has been used in China for pain and other conditions for over 3,000 years. There are no studies on the use of acupuncture in the pre-hospital setting.

Cold and Heat

Cryotherapy is defined as the therapeutic application of a substance (e.g. ice pack or coolant spray) to the body that removes heat from the body, resulting in decreased tissue temperature, while heat therapy is the therapeutic application of a substance (e.g. heat wrap, bath) to the body that adds heat, resulting in increased tissue temperature. The physiological effects of cryotherapy include reductions in pain, oedema, inflammation and muscle spasm, while the physiological effects of heat therapy include relief from pain and increases in blood flow and elasticity of connective tissues.

There is limited evidence to support the use of heat therapy in general; however, studies have shown heat-wrap therapy to provide short-term reductions in pain and disability in patients with acute low back pain.

Traction and Bracing

Skeletal traction is a common method for preoperative fracture stabilisation and pain control in patients with femoral shaft, acetabular and unstable pelvic fractures. Bracing may be useful to reduce pain and protect the neck, back and joints from further injury in trauma patients.

PHARMACOLOGICAL THERAPIES IN ACUTE PAIN

A wide range of analgesic agents are currently available for use in the ED and pre-hospital settings, including both opioid and non-opioid options with a number of different formulations and routes of administration. Determining which analgesic is the most appropriate to use in patients will depend on the setting in which the patient is presenting, the ability of the treating healthcare personnel to administer various analgesics, the pain intensity of the patient as determined by pain assessment and recommendations on the class of analgesic as provided by the WHO ladder.

1. **Paracetamol:** Used for treating mild-to-moderate acute pain, paracetamol can be administered intravenously (IV), per rectum (PR) or by oral routes. Paracetamol is often used in combination with opioids, and may decrease opioid requirements by up to 20%. The maximum recommended adult dose of paracetamol is 4000 mg/day and is for paediatric patients (toxic dose >200 mg/kg and maximum 80 mg/kg per day), with a risk of hepatotoxicity at higher doses. It should be used with caution in: Alcoholics; those at risk of hepatic dysfunction or with hepatic impairment; patients with cirrhosis; and those with renal impairment. Potential side-effects include hypersensitivity including skin rash, erythema, flushing, pruritus and tachycardia. Paracetamol is contraindicated in severe hepatic impairment or severe active liver disease.
2. **Non-steroidal anti-inflammatory drugs (NSAIDs):** Such as ibuprofen, diclofenac, ketorolac and naproxen are commonly used in both the pre-hospital and ED settings for mild-to-moderate pain, particularly with an inflammatory component. Most commonly administered via the oral or IV routes. NSAIDs inhibit the cyclo-oxygenase 1 (COX-1) and cyclo-oxygenase 2 (COX-2) enzymes in order to produce analgesic, antipyretic and anti-inflammatory effects. They may decrease opioid requirements and therefore opioid-related side-effects. However, they may also contribute to decreased fracture healing and infection and should not be used within the first 3 days of soft tissue injuries such as sprains or fracture to avoid potential delays to healing. They are associated with a number of serious adverse events including gastritis, bleeding and renal failure and should be avoided in the elderly. NSAIDs are contraindicated in patients with active peptic ulceration or those with stomach bleeding, uncontrolled hypertension, significant renal disease or impairment, those with inflammatory bowel disease such as Crohn's disease or ulcerative colitis and those who have experienced a previous transient ischaemic attack or stroke (apart from aspirin). Topical NSAIDs (most commonly diclofenac, administered via patches, plasters and gels) have been successfully used to provide relief in acute pain due to soft tissue injury and ankle sprain.
3. **COX-2 inhibitors** are a type of NSAID most typically used for the treatment of pain in arthritis and ankylosing spondylitis. They act to reduce pain and inflammation either by inhibiting COX-2 preferentially over the constitutive COX-1 or by inhibiting COX-2 only (Fig. 14.5). Currently, only four COX-2 inhibitors are available—etoricoxib, celecoxib, parecoxib and meloxicam. Etoricoxib is a COX-2 inhibitor available as an oral preparation in doses ranging from 30 to 120 mg which has demonstrated efficacy in acute tendinopathy, postoperative pain, for example, musculoskeletal pain. Celecoxib is a selective orally available COX-2 inhibitor used in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, primary dysmenorrhoea and adenomatous colorectal polyp pre-emptively before surgery to reduce postoperative pain scores. It is used as second line medication for acute pain besides paracetamol and NSAIDs such as ibuprofen. Parecoxib

is an injectable COX-2 inhibitor used for post-operative analgesia in adults, in renal colic and abdominal pain. Meloxicam, available as oral and dispersible preparations, inhibits both COX-1 and COX-2 with preference for COX-2 and is used almost exclusively for chronic pain conditions such as rheumatoid arthritis. It has a half-life of 20 hours and only reaches peak plasma concentrations after approximately 10 hours, rendering it of little use for emergency pain scenarios.

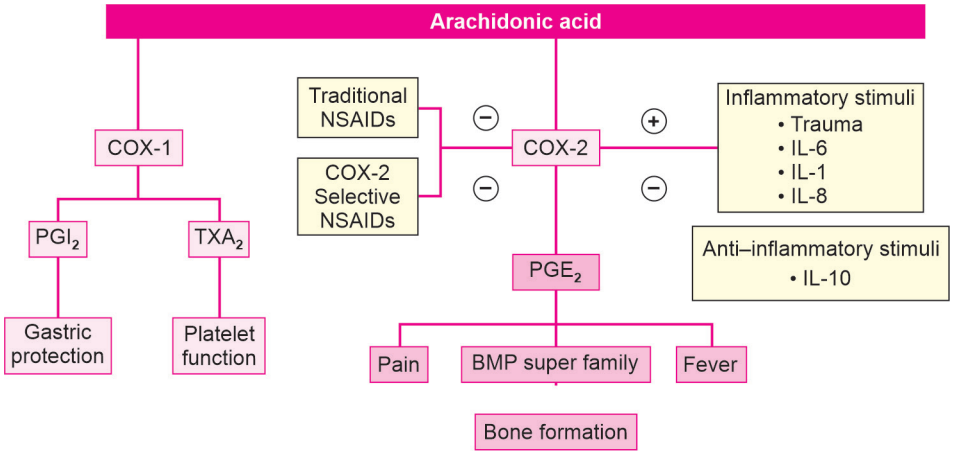


Fig. 14.5: COX-1, COX-2 pathway

4. **Opioids:** Act on opioid receptors, primarily within the central nervous system, to produce an analgesic effect. They are commonly used for treating moderate-to-severe acute pain, with weak opioids such as codeine or tramadol typically used for moderate pain, and strong opioids such as morphine and fentanyl typically used for severe pain.They can be administered via the intravenous (IV), intramuscular (IM), intranasal (IN), oromucosal (OM)/sublingual (SL), subcutaneous (SC) or oral routes, with the choice of opioid and route of administration depending on the severity of the pain and the condition and comorbidities of the patient. They are associated side-effects (particularly in opioid-naive patients), such as nausea and vomiting, sedation and respiratory depression, and itching and anaphylactoid reactions and are contraindicated or should be used with caution in patients with severe respiratory instability, acute psychiatric instability or uncontrolled suicide risk, those receiving drugs capable of eliciting life-limiting drug–drug interactions, and those seeking opioids for addiction purposes.
   - Codeine is indicated for the management of acute moderate pain in children aged over 12 years and adults whose pain is not relieved by analgesics such as paracetamol or ibuprofen. It is available as an oral formulation in tablets and suspension form. Improved understanding of codeine's pharmacogenomics and the risk of ultrafast metabolism has raised concerns about its safety and it is contraindicated in children aged less than 12 years.
   - Tramadol, is a weak opioid analgesic used to relieve moderate-to-severe pain in postoperative period, pain associated with labour and acute myocardial infarction, as well as for trauma pain in both the pre-hospital and ED settings. Tramadol is available in IV, SC, IM and oral formulations. Side-effects include low rates of respiratory depression, nausea,vomiting and dizziness may occur with tramadol; however, these can be reduced by slower IV infusion.

- Morphine is a strong opioid commonly used for severe pain in the ED and pre-hospital settings via IV, SC, IM and oral routes. Recommended as the standard analgesic for management of severe acute pain in emergency settings. Morphine is associated with nausea, vomiting and dizziness, but these effects can be reduced and managed by administering the drug by a slower IV infusion. When morphine given via patient-controlled analgesia (PCA) and as titrated boluses, it was found that patients who were in control of their analgesia had greater reductions in pain score while consuming similar amounts of morphine. These patients were also more satisfied with their method of pain relief.
- Fentanyl is a strong opioid used for treating severe pain in the ED and pre-hospital settings, and commonly administered as intranasal, oromucosal or IV formulations. Fentanyl delivered intranasally can be associated with epistaxis, accidental swallowing and blocked nose, which can result in suboptimal drug delivery and reduced analgesia. Fentanyl is also available as an oromucosal formulation, which can provide relief of acute orthopedic pain in the ED in 10 minutes. Oromucosal fentanyl can also be combined with nitrous oxide for fracture reduction in the ED.
- Sufentanil is a synthetic opioid, like fentanyl, but with five to eight times the potency. It has been successfully used via the IN route to treat patients with moderate-to-severe pain in the extremities and in children in a pre-hospital setting but is unlicensed for use in children so should not be used in children aged 18 years. Oromucosal sufentanil tablets have demonstrated significant effects in moderate-to-severe acute pain in the ED, with a few adverse effects.

5. **Nerve blockade:** Local and regional nerve blockade, using local anaesthetic agents injected directly onto or near the nerve (either as a single injection, multiple injections, or a continuous infusion), is increasingly being employed for a wide range of painful injuries and illnesses. The absence of systemic sedation with nerve block analgesia makes it easier to monitor the mental status of patients with head injuries, and can ease the transport and supervision of patients with acute trauma. The disadvantages include: Complexity and the invasive nature of the procedures and the training required to achieve and maintain proficiency. Adverse effects are rare, but include infection, nerve injury and intravascular injection. Local anaesthetics are contraindicated in patients with heart block or severe sinoatrial block with no pacemaker fitted, serious adverse reactions to previous local anaesthetic administration, concurrent treatment with Class 1 antiarrhythmic agents (e.g. quinidine), and prior use of amiodarone hydrochloride. In addition, local anaesthetics in nerve blocks are often co-administered with epinephrine in order to slow the rate of anaesthetic absorption, and epinephrine is contraindicated in patients with pheochromocytoma, hyperthyroidism, severe hypertension or severe peripheral vascular occlusive disease. Single-injection blocks are mainly performed for anaesthesia, whereas continuous peripheral nerve blocks are predominantly used for perioperative analgesia.
6. **Lidocaine:** It is a local anaesthetic which can be given via topical, IV and intra-articular routes. Data to support the use of IV lidocaine for acute trauma pain in the ED are currently limited. Topical lidocaine, delivered as a patch, has shown effectiveness in treating rib fracture pain.

7. **Ketamine:** N-methyl-D-aspartate antagonist is widely used in emergency acute pain and commonly used in combat scenarios. It is given via IV, IM and IN routes. At full dose (1.5–2.0 mg/kg IV), ketamine is used as an anaesthetic, while at lower sub-dissociative doses (0.5 mg/kg) it provides analgesia that can be opioid sparing. Ketamine has a wide therapeutic index, cardiovascular stability and no incidence of respiratory depression.
8. **Antispasmodics:** Anticholinergic—dicyclomine and PDase inhibitor—drotaverine have smooth muscle antispasmodic action. They can be used in intestinal, biliary, renal colics, abdominal cramps when no mechanical obstruction is present. Dose of dicyclomine is 20 mg oral/IM and drotaverine 40–80 mg, TDS. Dicyclomine is contraindicated in children below 6 months.

MANAGEMENT OF PAIN IN PRE-HOSPITAL AND HOSPITAL SETTINGS

Pain assessment in the pre-hospital setting tends to be associated with the clinical condition and level of alertness of the patient. Providing effective pain relief is an important endpoint in itself (Table 14.2).

Management of pre-hospital analgesia often includes providing pain relief for procedures carried out at the scene of the emergency, most commonly limb realignments in case of dislocations and splinting in the case of fracture, which often result in intense-to-severe pain and must be managed accordingly. Ketamine, nitrous oxide and opioids are commonly used

Table: 14.2: History of acute pain

Pain management	
Site of pain	• Primary location of pain
Causes of pain onset	• Including details of trauma or surgical procedures
Character of pain	• Type of sensation—sharp, burning, throbbing, etc. • McGill pain questionnaire-sensory and affective descriptors • Neuropathic pain questionnaire, e.g. NPQ, DN4, LANSS, pain DETECT, ID pain
Pain intensity	Intensity in different situations • At rest • On movement • Other temporal factors – Pain duration – Pain over time: Current, last week, highest intensity – Nature of pain—continuous, intermittent
Associated symptoms	• Symptoms, e.g. nausea, vomiting, sweating, palpitations
Effects on pain activities and sleep	• Interruptions in sleep, inability to carryout normal activities
Treatment	• Present and past medications (dose, frequency, efficacy, side effects) • Other treatment modalities • Previous consultations
Relevant medical history	• Previous, medical and coexisting pain

DN4: Douleur Neuropathique en 4 Questions; NPQ: Neuropathic pain questionnaire; LANSS: Leeds assessment of neuropathic symptoms and signs.

in the pre-hospital setting. Ketamine is often combined with morphine in patients with acute trauma pain, and can reduce morphine requirements in these individuals.

Whichever analgesic agent is selected for pre-hospital pain management, monitoring the effects of that analgesic on the patient is vital, and should include electrocardiogram, breathing, oxygen saturation, blood pressure (BP) and (optionally) capnography. Emergency equipment for airway management, ventilation, suction and resuscitation must be available in case of an adverse response.

Algorithms for treatment of undifferentiated acute pain in the emergency setting (Fig. 14.6)

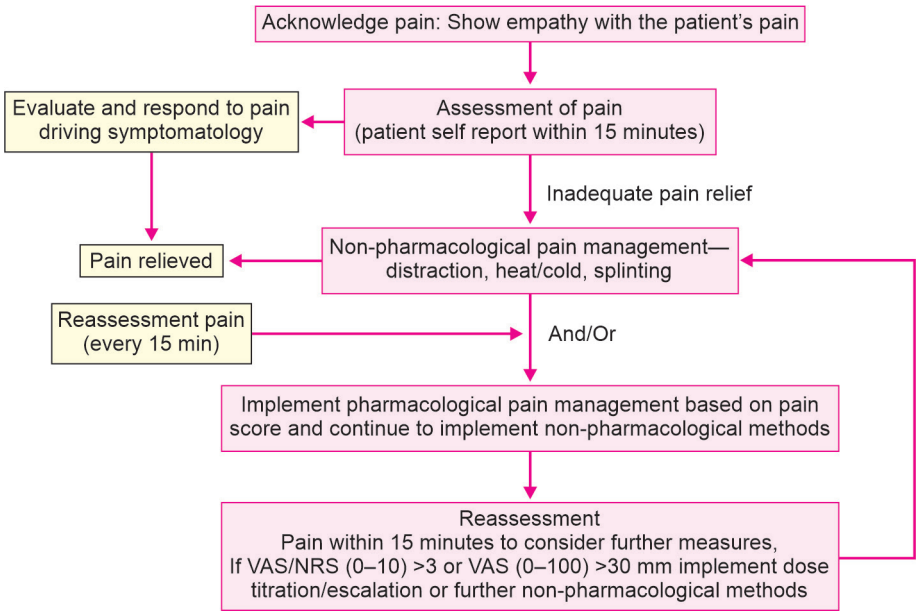

Acknowledge pain: Show empathy with the patient's pain
Assessment of pain (patient self report within 15 minutes)
Evaluate and respond to pain driving symptomatology
Inadequate pain relief
Non-pharmacological pain management—distraction, heat/cold, splinting
Pain relieved
Reassessment pain (every 15 min)
And/Or
Implement pharmacological pain management based on pain score and continue to implement non-pharmacological methods
Reassessment
Pain within 15 minutes to consider further measures,
If VAS/NRS (0–10) >3 or VAS (0–100) >30 mm implement dose titration/escalation or further non-pharmacological methods

Fig. 14.6: Management of acute pain symptoms

CHRONIC PAIN AND MANAGEMENT

INTRODUCTION

Acute pain resolves after tissue healing in most individuals. However, certain persons progress from acute-to-chronic pain, known as pain chronification. Although the processes underlying chronification are not yet well-understood, central nervous system changes to pain facilitation and inhibition are thought to play a role. The rates of pain chronification vary based upon the type of acute pain (e.g. low back, post-surgical, diabetic neuropathy). Other associated factors include: Maladaptive pain coping behaviours, co-occurring psychiatric illnesses, pain catastrophizing, a validated set of negative emotional/cognitive processes involving pessimism, perceptions of helplessness, and magnification of pain-related symptoms.

The American pain society (APS) initiated an influential campaign, "Pain, the fifth vital sign," to raise awareness among health professionals of pain assessment and management.

Recently, experts from the neurology and pain medicine have proposed a new definition as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (Table 14.3)."

Table 14.3: Causes of neuropathic pain		
Peripheral nerve	***Spinal cord***	***Brain***
Neuropathies	Traumatic injury	Stroke
Amputation	Vascular lesions	Multiple sclerosis
Traumatic injury	Multiple sclerosis	Syringobulbia
Entrapments	Avulsion injuries	Parkinson's disease
Herpes zoster	Syringomyelia	
Neoplastic invasion	Prolapse disc	Tumours
Nerve root disorders	Arachnoid—tumours	Abscesses

Other causes of neuropathic pain: Diabetes mellitus-induced peripheral neuropathy, postherpetic neuralgia, post-surgical chronic pain, post-chemotherapy, trigeminal neuralgia, peripheral radiculopathy, HIV, leprosy, stroke, chronic backache, chronic arthropathy, complex regional pain syndromes, entrapment neuropathy, etc.

Pathophysiology of Neuropathic Pain

Neuropathic pain is caused by damage to neural structures caused by inflammation, irritation or neural tissue compression. Neuropathic pain has been estimated to occur in as much as 7% of the general population. These chronic pain persistent syndromes offer no biological advantage and cause suffering and distress. Such maladaptive pain typically results from damage to the nerves—the peripheral nerves, the dorsal root ganglion of spinal cord and brain. Descriptors such as burning, lancinating numbness and electric shocks are more frequently encountered in chronic neuropathic conditions. Such symptoms comprise a complex combination of negative symptoms such as partial or complete loss of sensation and positive symptoms such as dysesthesia, paresthesia and shooting burning pain along the path of the affected nerve.

Common sensory abnormalities in these patients include hypo and hyperalgesia, allodynia, dysesthesia, paresthesia and spatiotemporal alterations (dyslocalization, radiation, after sensation, abnormal latency). In neuropathic pain after injury, symptoms are initially experienced distal to the site of injury. By contrast in nociceptive pain, symptoms are present at least initially, at the site of injury. As the time progresses, the margin between these types becomes blurred and one may co-exist with other type.

Motor dysfunction such as weakness and tremors is either a somatomotor reflex, a protective behaviour or a psychologically conditioned overlay. Majority of chronic neuropathies express themselves on a continuous nature with varying intensities, occasionally with superimposed intermittent or paroxysmal painful or non-painful symptoms. Exceptions are trigeminal neuralgia and glossopharyngeal neuralgia where pain is typically paroxysmal with a duration of a few seconds sometimes repeated hundreds of times a day.

Pathophysiology of Neuropathic Pain

Neuropathy is derived from Greek word, "*Neuro*"—meaning nerves and in general form indicating nerve disorders of any cause. It is not a specific disease but rather a manifestation of many conditions that cause damage to the nerves. Nerves may be injured or compressed by neighboring anatomic structures at a point along their course. In neuropathy, there may

be sensory, motor or mixed deficit. Neuropathy is divided into 3 main types as per nerve involvement.

Mononeuropathy—if only one nerve is involved.

Mononeuropathy multiplex—when damage to one or more different nerve areas.

Polyneuropathy—many nerves may be involved but the pattern is diffuse, symmetric and bilateral. On pathological basis neuropathy is of 2 types, i.e.

- **Axonal neuropathies**—in which predominant pathological feature is axonal degeneration.
- **Demyelinating neuropathies**—in which predominant pathological feature is paranodal or segmental demyelination.

Chronic Pain Management Guidelines

1. **Patient assessment and evaluation:** The goal of patient assessment and evaluation is to understand the nature, causes and severity of pain, and their impact on patient's functionality, mood and overall quality of life. The patient's health history should involve a review of: (a) patient's medications, including use and misuse; (b) allergies; (c) health and surgical history; (d) psychological health, including substance use and misuse; and (e) issues related to respiratory, cardiovascular, renal, hepatic, gastrointestinal, neurologic, endocrine, musculoskeletal and hematologic systems. A focused pain assessment and evaluation addressing pain symptoms, identification of pain risk factors and current and previous pain management, including physical and cognitive therapies, alternative modalities and response to these therapies should be done. Validated instruments should be used when appropriate to evaluate the patient's quality of life, physical, social, emotional functions and sleep quality.
2. **Management:** Non-pharmacologic management—they are safe and well tolerated, and when appropriate should be considered as part of treatment plan.

Non-pharmacological Management

- Physical rehabilitation modalities–therapeutic exercise, transcutaneous electric nerve stimulation, massage therapy, traction, cold and heat therapies, therapeutic ultrasound, bracing, touch therapy.
- Psychological and behavioural health approaches–cognitive behavioural therapies, psychological skills training (PST), mindfulness-based stress reduction programme.
- Complimentary approaches—yoga, tai chi, acupuncture.
- Other modalities—cryoneurolysis

Pharmacologic approach should be tailored to patient's health status (e.g. cardiovascular, renal, hepatic and cognitive issues) due to potential for drug side-effects, drug clearance, drug–drug interactions, patient's type of pain (neuropathic *vs* nociceptive), level of pain, functionality and response. Patient should be assessed and treated for disturbed sleep or depressed or anxious mood that may help increase response to treatment.

Pharmacological Management of Neuropathic Pain

Non-opioid modalities should be used as first line of treatment for chronic pain. Consider opioid therapy only if benefits outweigh the risk and patient is not responsive to other pharmacologic and non-pharmacologic treatment modalities. They should be used at the lowest effective dose and the shortest duration of time to achieve adequate pain control, with the intention of mitigating negative side-effects and opioid addiction risk.

Pain management will begin with a concerted effort to identify the etiology of the neuropathy, as directed therapy may help alleviate the symptoms. Algorithm for the diagnosis and treatment of neuropathic pain is designed by merging recommendation/guidelines based on published literature for neuropathic pain (Table 14.4).

Table 14.4: Treatment modalities for Chronic pain management

Strategy	*Examples*	*Dose range*	*FDA-approved chronic pain indications*	*Side effects*
Multidisciplinary approach	Johns Hopkins Hospital Pain Treatment Program	3–4 weeks of intensive 5–7 days/week attendance at clinic	Not subject to FDA approval. Has shown improvement in chronic pain with no identifiable cause	None
Non-opioid medications	NSAIDS (a) Aspirin	325–650 mg every 4 h (max. 4 g/day)	Disorder of joint of spine, generalised pain, headaches, osteoarthritis (OA), rheumatoid arthritis (RA)	Bleeding, gastric ulcer, tinnitus, bronchospasm, Reye's syndrome
	(b) Ibuprofen	200–800 mg every 4–6 h (max. 3.2 g/day)/ 250–500 mg BD (max. 1 g/day)	Generalised pain, headaches, OA, RA	CHF, MI, stroke, Stevens-Johnson syndrome, hearing loss
	(c) Naproxen	30–60 mg/day	Ankylosing spondylitis, bursitis	CHF, MI
	Antidepressants (a) Duloxetine	60 mg OD	Diabetic peripheral neuropathy, fibromyalgia, chronic musculoskeletal pain	Suicidal ideation, Steven-Johnson syndrome, MI, liver failure, serotonin syndrome
	Anti-epileptic drugs (a) Gabapentine	300–600 mg TDS	Post-herpetic neuralgia	Steven-Johnson syndrome, hypoglycaemia, sedation, suicidal thoughts, dizziness, abuse potential
	(b) Pregabalin	75–150 mg BD (max. 450 mg/day)	Diabetic peripheral neuropathy, fibromyalgia, neuropathic pain from spinal cord injury, post-herpertic neuralgia	Jaundice, suicidal thoughts, acute renal insufficiency
Physical therapy (PT)	Exercise therapy	8–12 PT sessions over 4–6 weeks	Not subject to FDA approval. Used to treat back and neck pain, arthritis, fibromyalgia	Worsening pain, MI, sudden death
Psychosocial therapy	Cognitive behavioural therapy	Weekly hour long individual sessions for 12 weeks	Not subject to FDA approval. Used for all types of pain	None

Contd.

Table 14.4: Treatment modalities for Chronic pain management

Strategy	*Examples*	*Dose range*	*FDA-approved chronic pain indications*	*Side effects*
	Mindfulness based stress reduction	Weekly 2 h long group sessions for 8 weeks	Not subject to FDA approval. Used for all types of pain	None
Complimentary and alternative medicine	Acupuncture	6–12 sessions over 6–12 weeks	Not subject to FDA approval. Used for OA, chronic pelvic pain, chronic prostatitis, chronic neck and back pain	Nerve injury
Peripheral procedure	(a) Trigger point injection Lidocaine, corticosteroids or dry needling	Single injection, may be repeated	Not subject to FDA approval. Used in chronic neck pain, headaches, iliac crest pain, myofascial syndrome	Nerve injury, pneumothorax, seizures, local tissue necrosis
	(b) Intra-articular injection Sodium hyaluronate, corticosteroids	Single injection. May be repeated	Not subject to FDA approval. Used for OA, RA, hip arthritis, low back pain, shoulder pain, de Quervain's tenosynovitis	Nerve injury
Spinal procedures	Epidural steroid injection	1–3 injections separated by at least a month (no more than 3 injections in 12 months)	None	Infection, bleeding, vertebral fractures, paralysis, stroke, loss of vision, death
	Nerve block	One diagnostic block and then second long-term nerve block (3–6 months pain relief)	Chronic radiculopathy, cancer related, facet joint degeneration	Nerve injury, infection, paralysis and seizure
	Radio frequency denervation	1–2 diagnostic nerve blocks followed by fluoroscopic-guided destruction of nerve	Facet joint pain, low back pain with disc herniation, sacroiliac pain	Nerve injury, infection, paralysis and seizure
	Spinal cord stimulator	Insertion of temporary stimulator to determine efficacy and then insertion of permanent device	Chronic intractable pain of the trunk and/or limbs, pain associated with failed back surgery syndrome, complex regional pain syndrome	Nerve injury, infection, paralysis and seizure
Surgery	Discectomy, spinal fusion		Back pain with nerve injury (disc herniation), spinal stenosis	Failed back surgery syndrome, death, paralysis, infection

Diagnosis

This forms the first step in management. A proper history and clinical examination is an essential tool to diagnosis and treatment of neuropathic pain and neuropathies. There are several factors that cause or exacerbate the chronic pain. Patient may have a disease that is painful, e.g. arthritis, cancer, migraine headache, fibromyalgia and diabetic neuropathy. Secondly, there may be perpetuating factors that are initiated by bodily disease and persist after the disease has resolved, e.g. damaged sensory nerves, sympathetic efferent activity and painful reflex muscle contractions.

Inquiry should be made about recent viral infections, starting of new medications, exposure to toxins, pesticides or heavy metals, occurrence of similar symptoms in family members or coworkers, habit of alcohol consumption etc. Relevant enquiry should be made about how pain first appears, how it progresses, if pain is worse at night or if pain is triggered by minor irritation.

The physical examination for neuropathic pain should include evaluation of tone, strength, reflexes, sensation, and vasomotor/sudomotor activity. It requires a paperclip or pin to test "pinprick" sensation, a cotton ball or fingers to test "light touch". Palpation of the entire course of the nerve in question should be a part of the examination.

Investigations

To establish the fact that pain is due to neuropathy, one may have to perform some investigations. These include standard lab investigations, electromyography (EMG) and nerve conduction velocity studies (NCS), magnetic resonance imaging (MRI) and nerve biopsy.

Standard lab investigations—include complete blood counts, erythrocyte sedimentation rate (ESR), urinalysis, chest X-ray, postprandial blood sugar levels, serum protein electrophoresis, antinuclear antibodies, rheumatoid factor, cerebrospinal fluid (CSF) examination for cells, protein, sugar and serology.

Electromyography—can detect denervation, which is indicated by the presence of fibrillation potentials, and have positive waves at rest and decreased number of motor unit potentials.

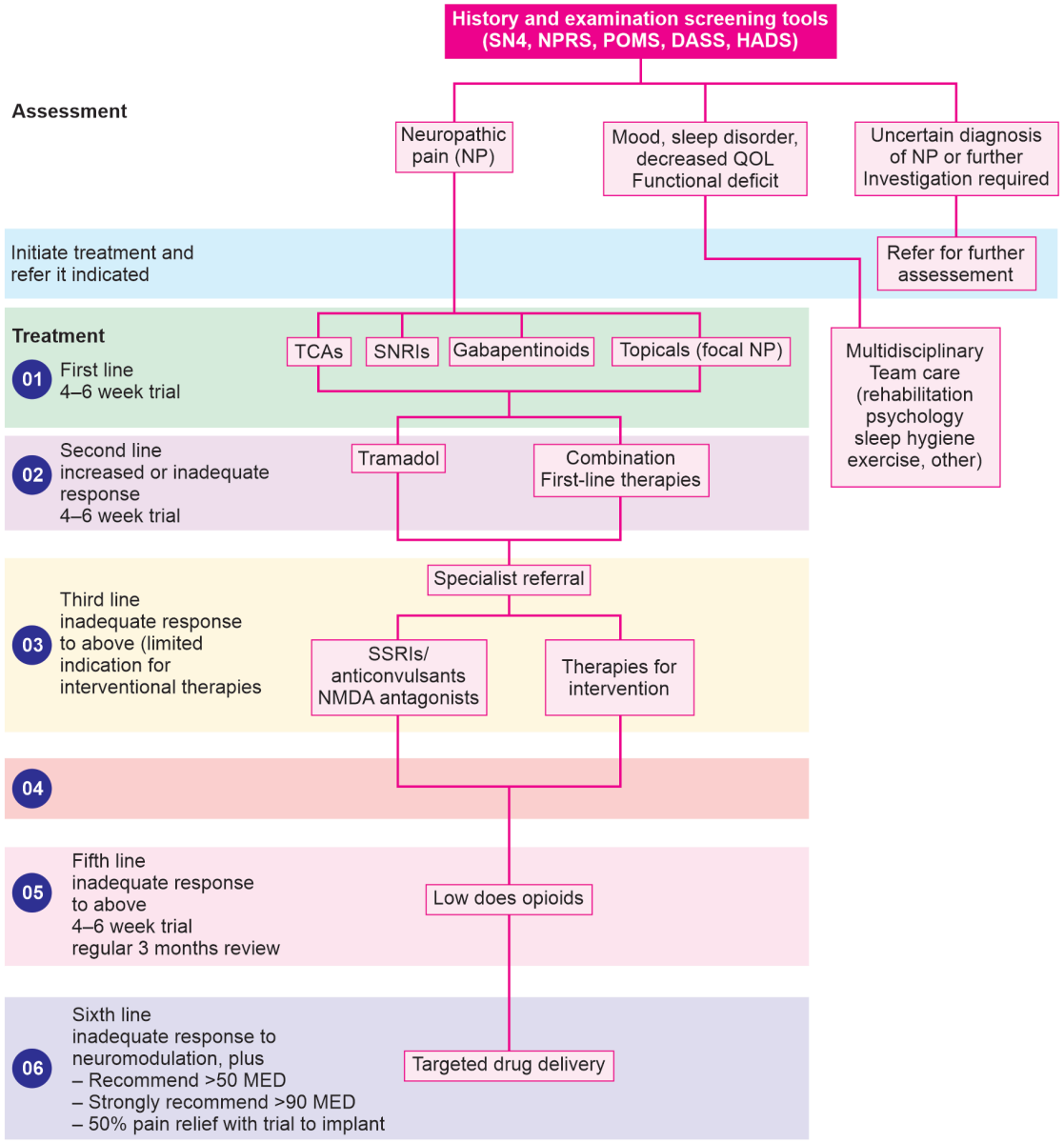
Nerve conduction studies (NCS)—can identify nerve damage, in most cases distinguish demyelinating neuropathy from axonal neuropathy and also give valuable information about the distribution of nerve lesions including area of focal nerve compression.

MRI—can be used to identify structural neurological lesions.

Nerve biopsy: Structural nerve at the ankle is preferred site for cutaneous nerve biopsy. Immunohistochemistry stained epidermal nerve fiber study in small punch biopsies of skin is another valuable tool.

General principles and supportive measures: Neuropathic pain, due to its accompanying neuropathy may occur along with motor dysfunction. So, physiological exercises are important to prevent muscle contractures and keep it mobile and earlier practice of splinting to be discouraged. Anesthetic extremities are to be protected from injuries. Such behavior as leaning on elbows or sitting with crossed legs for lengthy periods are to be avoided. Additional organ injury may occur at prime points. Use a frame to reduce contact with bedclothes. For associated autonomic dysfunction such as postural hypotension, waist high elastic stockings can be used to prevent venous pooling and augment venous return.

Treatment of neuropathic pain: The treatment modality can be subdivided into pharmacological pain management and interventional pain management (Fig. 14.7).


History and examination screening tools (SN4, NPRS, POMS, DASS, HADS)
Assessment
Neuropathic pain (NP)
Mood, sleep disorder, decreased QOL Functional deficit
Uncertain diagnosis of NP or further Investigation required
Initiate treatment and refer it indicated
Refer for further assessement
Treatment
01 First line 4–6 week trial
TCAs
SNRIs
Gabapentinoids
Topicals (focal NP)
Multidisciplinary Team care (rehabilitation psychology sleep hygiene exercise, other)
02 Second line increased or inadequate response 4–6 week trial
Tramadol
Combination First-line therapies
Specialist referral
03 Third line inadequate response to above (limited indication for interventional therapies
SSRIs/ anticonvulsants NMDA antagonists
Therapies for intervention
04
05 Fifth line inadequate response to above 4–6 week trial regular 3 months review
Low does opioids
06 Sixth line inadequate response to neuromodulation, plus – Recommend >50 MED – Strongly recommend >90 MED – 50% pain relief with trial to implant
Targeted drug delivery

Key/legend

DASS : Depression anxiety stress scales
DN4 : Douleur neuropathique 4
HADS : Hospital anxiety and depression scale
MED : Morphine equivalent dose
NPRS : Numeric pain rating scale
POMS : Prolle of mood states
QOL : Quality of life
SNRIs : Serotonin and noreplnephrine reuptake inhibitors
SSRIs : Selective specific reuptake inhibitors
TCAs : Tricyclic antidepressants

Fig. 14.7: Algorithm for the management of neuropathic pain

Pharmacological Pain Management

1. Antidepressants

Antidepressants enhance the descending monoaminergic inhibitory pathways via central blockade of serotonin and noradrenalin reuptake process. Drugs are tricyclic antidepressants (TCAs), selective serotonin re-uptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

Tricyclic antidepressants (TCA)—are first-line drugs for the treatment of neuropathic pain. TCA consisting of tertiary amines—amitriptyline, imipramine, trimipramine, clomipramine, doxepin and their demethylated secondary amines—nortriptyline, desipramine, protriptyline and amoxapine. TCA are quite effective in the treatment of severe persistent pain due to malignant tumours, post-herpetic neuralgia, trigeminal neuralgia, diabetic peripheral neuropathy, migraine/headache, rheumatoid arthritis, post-spinal cord injury neuropathic pain, chronic low back pain and cancer. Commonly used TCA (amitriptyline, nortriptyline and desipramine) daily dosage are same and start at 10–25 mg per oral, increase on weekly basis to maximum daily dose 150 mg.

TCAs have multiple modes of action, with the most important pain-relieving effect likely being via inhibition of serotonin and noradrenaline re-uptake. However, they also block histamine, adrenaline, acetylcholine, and sodium channels, accounting for their broad side effect profile. Most common side-effects are dry mouth, constipation, sweating, dizziness, blurred vision, drowsiness, palpitation, orthostatic hypotension, sedation and urinary retention. They also cause cognitive disorders, gait disturbance and falls, particularly in elderly patients.

Serotonin-norepinephrine reuptake inhibitors (SNRIs), capable of inhibiting both serotonin-norepinephrine reuptake pump, are effective in various types of neuropathic pain. Two SNRIs are commonly used—duloxetine and venlafaxine.

Duloxetine—it is the first line drug to treat the patients with peripheral diabetic neuropathy (PDN), fibromyalgia, musculoskeletal back pain and osteoarthritis. Main advantage over TCA is, it is devoid of anticholinergic and cardiac side-effects. Starting dose should be 30 mg/day to avoid nausea and titrated after one week to 60 mg/day.

Venlafaxine—is another drug of SNRIs class, start with dose of 37.5 mg to maximum daily dose 225 mg is shown to be effective against neuropathic pain.

2. Antiepileptics

In certain respects, epilepsy and neuropathic pain resemble each other. Injured sensory fibers may discharge spontaneously. Antiepileptic drugs by blocking this, may have analgesic effect in neuropathic pain. Enormous literature is available to support the role of antiepileptics in paroxysmal nocturnal hemoglobinuria (PNH), trigeminal neuralgia, painful diabetic neuropathy. Antiepileptics used for neuropathic pain are phenytoin, valproate, carbamazepine, oxcarbamazepine, gabapentinoids (gabapentin and pregabalin), newer anticonvulsants including lamotrigine and topiramate.

Phenytoin—was the first anticonvulsant to be used in neuropathic pain. In 1942, phenytoin was reported by French physician to be efficacious in the relief of trigeminal neuralgia and is the mainstay of treatment for two decades. Phenytoin acts by having sodium channel blocking effect. For neuropathic pain, relief dose of 200–500 mg/day is required. Adverse effects include

gum hypertrophy, hirsutism, and megaloblastic anemia, osteomalacia, hyperglycemia, allergic reactions include rashes, discoid lupus erythematosus (DLE) and neutropenia.

Carbamazepine: It has proven to be having particularly dual mode of action, i.e. blockade of sodium channels and potentiation of GABAergic neurotransmission. Carbamazepine has proven to be particularly effective against trigeminal neuralgia, glossopharyngea neuralgia, post-herpetic neuralgia and diabetic neuropathies. Dosage starts with 100 mg twice daily and then increase it gradually in 100 to 200 mg incremental doses to maximum dose up to 1600 mg for adequate pain relief. Side-effects includes dizziness, ataxia, nystagmus, confusion and lethargy, hyponatremia, skin rashes, drug-induced hepatitis and thrombocytopenia, rarely leukopenia and aplastic anemia due to bone marrow suppression. Liver function tests, serum sodium, and complete blood count monitoring is required.

Oxycarbamazepine—is an analogue of carbamazepine, which rapidly reduces to its active metabolite. Effects are equivalent and idiosyncratic reactions are rare. Dosage 1200 to 1800 mg/day.

Gabapentinoids (gabapentin and pregabalin)—are considered first-line agents in the treatment of neuropathic pain.

Used mainly in post-herpetic neuralgia, painful diabetic neuropathy and spinal cord injury. They act by blocking presynaptic voltage-gated calcium channels in the dorsal horn, inhibiting neurotransmitter release such as substance P, glutamate, and norepinephrine.

Gabapentin—exhibits saturable absorption that makes its pharmacokinetics less predictable. It is minimally protein bound (<3%), and is excreted from the kidneys as an unchanged drug. Dosage adjustment should be done according to individual creatinine clearance in case of patients with renal impairment. Treatment should be initiated at low dose and slowly increased. Effective dosage for gabapentin ranges from 1800 to 3600 mg/day (administered in three divided doses). Generally, two weeks are required to observe the effect, although several weeks are needed for titration. Dizziness, somnolence, peripheral edema, weight gain and dry mouth are the most common side-effects.

Pregabalin—is an analogue of gabapentin and has higher affinity for the presynaptic calcium channel in comparison to gabapentin. Pregabalin is as effective as gabapentin, however at much lower doses. Recommendation is to start with dose 75 mg/day at bed time and slowly increased to effective dose range 150 to 600 mg/day in two divided doses over 1–2 weeks. Pregabalin is associated with increase in suicidal behavior and ideation, and patients taking this medication should be monitored for any abnormal changes in mood and behavior.

Lamotrigine—is newer antiepileptic drug effective in NP from refractory trigeminal neuralgia, HIV neuropathy and central poststroke pain. Lamotrigine acts by blocking voltage-gated sodium channels, by preventing release of glutamate. Recommended daily dose is 50 mg for 15 days, increased to twice daily for another 15 days going more up to 400 mg/day. Reported side-effects are skin rashes, ataxia, diplopia, and at times intense reaction.

Topiramate—is another newer antiepileptic drug used only in diabetic neuropathic condition in doses 200 to 400 mg/day. Weight loss and withdrawal effects are reported at higher doses.

3. Topical Lidocaine and Capsaicin

The side-effect profile of TCAs, SNRIs, and gabapentanoids requires extremely cautious dosing in many patients, especially the elderly, with some patients having side-effects with

the lowest available doses. As an alternative, topical medications are supported by multiple guidelines, but its effectiveness varies. The topical preparations are limited to lidocaine patches and capsaicin.

Topical lidocaine: Works by decreasing ectopic firing of peripheral nerves. It is recommended as first line or second-line for the treatment of focal neuropathic pain such as post-herpetic neuralgia. 5% lidocaine patch application cause modest decrease in pain and well-tolerated by the elderly.

Topical capsaicin: Has its action through binding to the TRPV1 receptor located on the Aδ and C-nerve fibers. This results in release of substance P and depolarization of the nerve. Long-term exposure causes overstimulation, depletion of substance P, desensitization of the nerve, and reversible nerve degeneration. High concentration capsaicin (8%) is recommended as an alternative in focal neuropathic pain for those who "wish to avoid, or who cannot tolerate, oral treatments". Topical capsaicin is painful on initial application, and its efficacy depends on regular consistent use, thus making compliance with a capsaicin-based regimen challenging in many patients. It has been used successfully in post-herpetic neuralgia, HIV-related peripheral neuropathy and painful diabetic neuropathy.

4. Opioids

Opioids are reserved for prompt relief of pain during titration of first-line medications or pain relief failed with first-line regimen, for episodic discharges in severe chronic pain and for neuropathic pain of cancer. Common side-effects are nausea, vomiting, constipation, sedation and respiratory depression. Common drugs being used are morphine, fentanyl, tramadol, oxycodone and methadone. Use of oral methadone and transdermal fentanyl has yielded results in terms of pain relief in patients with reflux sympathetic dystrophy and severe neuropathic pain.

Tramadol—is a weak opioid agonist and mimics some of the properties of the TCAs in that it inhibits re-uptake of noradrenalin and serotonin. Tramadol has shown significant benefit in painful diabetic neuropathy and mixed neuropathic syndromes. Tramadol leads to less constipation and nausea than other weak opioid analgesics, such as codeine.

Tapentadol—is a newer opioid analgesic, pharmacologically similar to tramadol in that it has a dual mechanism of action, but has higher affinity for the μ-opioid receptor and has only noradrenergic activity as a monoamine re-uptake inhibitor. Tapentadol is approximately one-fifth as potent as oxycodone and has shown efficacy in the management of painful diabetic neuropathy, with greater tolerability.

5. N-methyl-D-aspartate (NMDA) Receptor Antagonists

NMDA receptors play an important role in central sensitization and thus are positive target of action for various drugs. Present data are still conflicting about the efficacy of NMDA antagonists in NP. Ketamine and dextromethorphan are the two most studied NMDA receptor antagonists in NP.

Dextromethorphan—it is a non-competitive NMDA antagonist, effective in neuropathic pain, provides relief in heat hyperalgesia and in mechanical allodynia. Dextromethorphan 400 mg/day is effective in patients with peripheral diabetic neuropathy.

Ketamine has good analgesic effect in neuropathic pain but its use is associated with side-effects—somnolence and dizziness.

Memantine—has low side effect profile owing to its rapid blocking/unblocking kinetics at the NMDA receptors (NMDARs).

6. Standard Analgesics Like Aspirin, Acetaminophen and Mechanism of Action

Non-steroidal anti-inflammatory drugs (NSAIDS) are used particularly for mild-to-moderate headache and for pain of musculoskeletal in origin. Mechanism of action is inhibition of the enzyme cyclo-oxygenase except for acetaminophen. Gastric irritation is a common side-effect of NSAIDs. Prolonged use can lead to GIT bleeding and ulceration which can be prevented by use of PPIs (omeprazole 20–40 mg, orally, daily). Celecoxib should be used with caution in patients with cardiac disease. Presently, role of NSAID in neuropathic pain is limited.

7. Botulinum Toxin

Botulinum toxin is a potent neurotoxin used for the treatment in spasticity, focal dystonia and chronic migraine pain. Studies show benefit in the treatment of peripheral neuropathic pain in diabetic neuropathic pain, spinal cord injury, complex regional pain syndrome (CRPS), post-herpetic neuralgia and trigeminal neuralgia with minimal side-effects.

INTERVENTIONAL PAIN MANAGEMENT

1. **Neural blockade:** The perineural injection of drugs seems to produce pain relief in some patients with neuropathic pain for varying length of time. Local anesthetic may give only short-term relief. Addition of corticosteroids may lengthen the pain relief. Corticosteroids also reduce inflammation by decreasing PG synthesis. They suppress ectopic discharge, have membrane stabilizing effects and stabilize the dorsal horn cell and these effects may contribute to pain relief. Absolute alcohol, 6% phenol or anhydrous glycerol can also be used as neurolytic agent. Neural blockade frequently used in clinical practice are percutaneous retrogasserian glycerol rhizolysis for trigeminal neuralgia, stellate ganglion blocks for CRPS, epidural steroid injections for persistent lumbosacral radiculopathy and nerve blocks for post-herpetic intercostal neuralgia.
2. **Electric stimulation:** Electric acupuncture has long been used to relieve pain by controlling the activity of autonomic nervous system (ANS).
3. **Surgical intervention:** In dorsal root entry zone lesions, dorsal rhizotomy and cordotomy are some of the procedures done in relieving chronic intractable pain, with its hazards of uncomfortable neurological complications which occurs after ablation. Compressive neuropathic pain syndromes like carpel tunnel syndrome, tarsal tunnel syndrome get good pain relief with surgical decompression.
4. **Implantable devices:** Intrathecal grafting of cells as biological pumps is being used. These pumps deliver monoamines, endorphins and trophic factors has been shown to be effective in treating chronic pain states both in experimental animals and in clinical trials. Intrathecal neuroblastoma cells are particularly suitable for heat hyperalgesia and cold algesia.

FUTURE TRENDS

Due to the success in making animal models for neuropathic pain and due to better understanding of the mechanism of neuropathic pain and receptors, many new drugs are found very effective in neuropathic pain. As receptors and transmitters involved in producing

various components of neuropathic pain have been identified, in coming years, drugs for specific type of neuropathic pain may come in use. Various types of drugs on which research is being conducted includes newer anticonvulsants, flebamate, N type calcium channel blockers, nootropic drugs and gene therapy.

MIGRAINE

It is characterized by hemicranial headache with accompanying aura (visual or auditory hallucinations), déjà vu phenomenon (repeated flashes of episodes) The aggravating factors are decreased sleep and skipping of meals. If an ophthalmic examination shows normal fundus and ENT examination reveals normal ear ossicles, the diagnosis is migraine.

Mild migraine: Fewer than one attack per month of throbbing but tolerable headache. Simple analgesics like 500 mg—1 g paracetamol; aspirin—75 mg, BD taken at the first indication of an attack and repeated 6 hourly.

Moderate migraine: When the throbbing headache is more intense lasting for 24 hours with nausea, vomiting and functional impairment. NSAIDs—ibuprofen (400 mg BD), naproxen (500 mg, BD), diclofenac (50 mg, 8 hourly), mephenamic acid (500 mg, TDS). They reduce inflammation around the cerebral, cranial vascular tissue. Drugs are taken only till the attack passes off. Antiemetics like metoclopramide is frequently used.

Severe migraine: These patients suffer 2–3 or more attacks per month of severe throbbing headache lasting 12–48 hrs, often accompanied with vertigo, vomiting, and aura. The specific antidotes are ergotamine, dihydroergotamine and tryptans. The ergot preparations reduce neurogenic inflammation and leakage of plasma in duramater that occurs due to retrograde stimulation of perivascular afferent nerves. Ergotamine is started at 1 mg, oral and repeated every 30 minutes till headache is relieved up to 6 mg maximum to prevent serious toxic effects of vasoconstriction. Dihydroergototamine (DHE) constricts the venules and preferred over ergotamine as 2–6 mg oral dose to maximum of 10 mg.

Sumatriptan is selective 5H1D/1B presynaptic receptor agonist. It constricts dilated cranial blood vessels epecially the arteriovenous shunts in the carotid artery. Dilation of these shunt vessels during migraine diverts blood flow away from brain parenchyma. It may inhibit inflammatory neuropeptide release around the affected vessels and extravasation of plasma proteins across dural vessels. The dose of tryptans–sumatriptan/almotriptan is 25/50 mg, BD. The other tryptans are zolmitriptan, naratriptan, rizatriptan, frovatriptan. They are highly effective and should be administered at the earliest during acute attack. Oral route is convenient. In case of nausea and vomiting, sumatriptan 6 mg, SC provides relief. Their effect is over before headache subsides completely except in case of naratriptan and frovatriptan. Sumatriptan may cause bitter taste, stinging burning sensation, mild pain at the site of injection. Oral use may cause paresthesia, asthenia, fatigue, tightness over the chest, jaw and neck, drowsiness, nausea and vomiting. It is contraindicated in ischemic heart disease, hepatic or renal impairment and pregnancy.

Zolmitriptan is used as nasal spray for children >12 years for acute migraine. Frovatriptan is preferred in menstrual migraine.

Drug interactions: Triptans should not be used concurrently or within 24 hours with ergot alkaloids. Caffeine increases absorption of ergotamine. So, used.

Prophylaxis of migraine: If headache—3–4 episodes/month, then ABCD (all 4 drugs) are given.

Tricyclic antidepressants (TCA)—amitriptyline (25–50 mg, HS) is effective in many patients and produces more side-effects than propranolol.

β **blockers:** Propranolol reduces frequency and severity of attacks in 70% patients. The starting dose is 40 mg, BD, but may be increased to 160 mg, BD.

Calcium channel blockers: They benefit migraine by reducing intracellular Ca overload due to brain hypoxia. Flunarizine. Dose 5–10 mg, OD.

Anticonvulsants: Valproic acid (400–1200 mg/day)/Gabapentin (300–1200 mg/day)/ Topiramate (25–50 mg, OD) are used in patients refractory to other drugs.

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Chapter
15

Treatment of Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disease that occurs after the age of 65 years and considered senile dementia. It is estimated that close to 50 million people worldwide are affected by dementia due to AD and the prevalence of the disease is likely to more than double by 2050.

ETIOPATHOGENESIS

Increasing age, low education, presence of epsilon 4 allele of apoprotein E on chromosome, 19, female gender, Down's syndrome, head injury in the past, homocyteinemia, hypercholesterolemia a family history of dementia are well-established risk factors of Alzhiemer's disease.

The histopathology comprises of neuronal loss and deposits of intraneuronal amyloid plaques and intracellular neurofibrillary tangles. Pathology of AD is characterized by extracellular amyloid plaques, intracellular neurofibrillary tangles, and nerve cell death. Amyloid plaques are composed of amyloid-β (Aβ), a cleavage product of the amyloid-β protein precursor (AβPP).

Aβ monomers progressively aggregate into oligomers, fibrils, and insoluble amyloid plaques. Amyloid accumulates abnormally in brain and interferes with normal brain functioning. Neurofibrillary tangles consist of hyperphosphorylated tau proteins. Tau proteins play an important role in holding neurons together. In AD, the tau proteins break loose from the neurons and are heavily phosphorylated and that microtubules are lost in AD.

The amyloid cascade hypothesis of AD poses that accumulation of Aα dysregulates synaptic and neuronal function, creating the intracellular conditions for formation of neurofibrillary tangles, leading to neuronal loss and further compromise of neurotransmitter function. Loss of cholinergic neurons in the basal forebrain (and consequent loss of signaling) is hypothesized to create a cholinergic deficit contributing to short-term memory loss in AD.

Clinical Presentation (Fig. 15.1)

The normal

1. **Pre-symptomatic stage** can last for several years or more. This stage is characterized by mild memory loss and early pathological changes in cortex and hippocampus, with no functional impairment in the daily activities and absence of clinical signs and symptoms of AD.

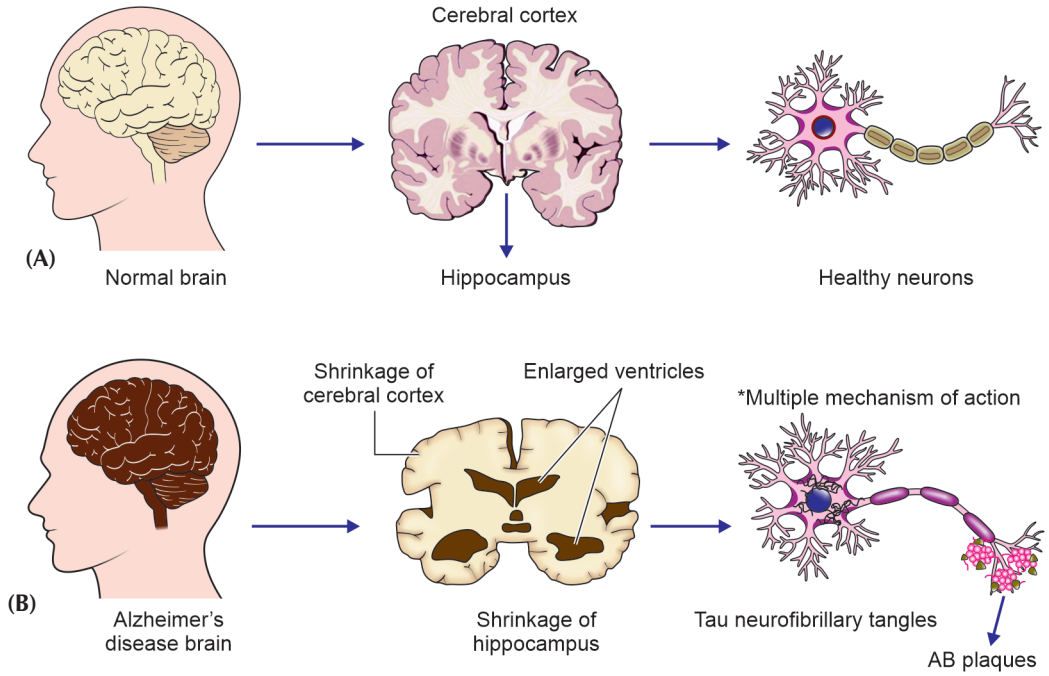

Fig. 15.1: Pathological changes in Alzheimer's disease

2. **Mild or early stage of AD** where several symptoms start to appear in patients, such as trouble in the daily life of the patient with a loss of concentration and memory, disorientation of place and time, a change in the mood, and development of depression.
3. **Moderate AD stage** in which the disease spreads to cerebral cortex areas that results in an increased memory loss with trouble recognizing family and friends, a loss of impulse control, and difficulty in reading, writing, and speaking.

   Summarising these 3 stages, the patient has abnormalities of memory, problem solving, language calculation, visuospatial perception, judgement and behaviour, delusions and hallucinations in some. All these patients suffer from impairment of mental functions and activities of daily living.
4. **Severe AD or late-stage** involves the spread of the disease to the entire cortex area with a severe accumulation of neuritic plaques and neurofibrillary tangles, resulting in a progressive functional and cognitive impairment where the patients cannot recognize their family at all and may become mute, incontinent, bedridden with difficulties in swallowing and urination eventually leading to the patient's death due to these complications (Fig. 15.2).

TREATMENT

There is no specific treatment and primary focus is on amelioration of associated behavioural and neurological problems. Even though AD is a public health issue, presently, there are only two classes of drugs approved to treat AD, including inhibitors to cholinesterase enzyme and antagonists to N-methyl-D-aspartate (NMDA).

1. **Cholinesterase inhibitors (AChEIs):** According to the cholinergic hypothesis, AD is due to the reduction in acetylcholine (ACh) biosynthesis. Increasing cholinergic levels

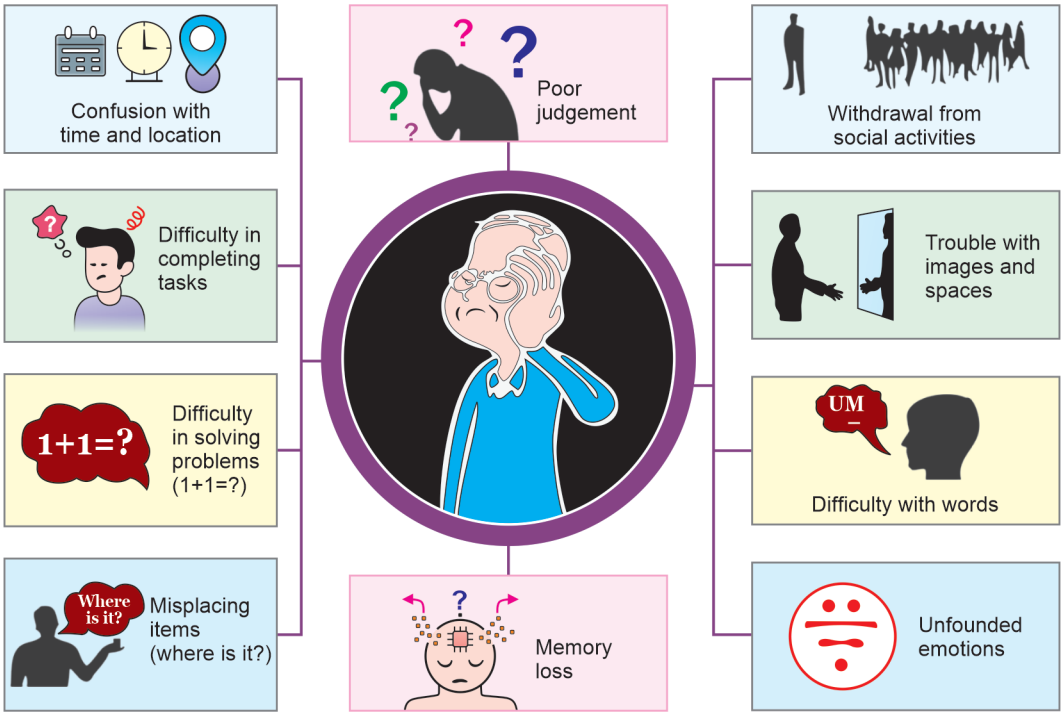

Fig. 15.2: Clinical presentation in Alzhiemer's disease

by inhibiting acetylcholinesterase (AChE) is considered one of the therapeutic strategies that increases cognitive and neural cell function. Most common AChEIs for AD patients in clinical use are tacrine, donepezil, rivastigmine, and galantamine.

Tacrine (tetrahydroaminoacridine) is the first FDA approved cholinesterase inhibitor drug for the treatment of AD. Start with initial dose of 40 mg/day (10 mg QID) for 4 weeks, then on monthly basis increase up to 160 mg/day to have desired effect. Side-effects are dose-related. The most common are nausea, vomiting, diarrhoea and hepatotoxicity, necessitating frequent testing of liver function and adjustment of the dose or switch to other medication.

Donepezil is long-acting piperidine inhibitor of acetylcholinesterase. The drug is well-tolerated with mild and transient cholinergic side-effects of the gastrointestinal and nervous systems. Donepezil is used to treat symptoms of AD such as improving cognition and behavior without altering the AD progression. Start with 5 mg, increase on monthly basis to 20 mg/day to have desired effect.

Rivastigmine is a carbamate and pseudo-irreversible inhibitor of AChE and butyrylcholinesterase (BuChE) that acts by binding to the two active sites of AChE (anionic and estearic sites), which results in preventing ACh metabolism. Rivastigmine dissociates more slowly than AChE, which is why it is called a pseudo-irreversible. The drug is used in mild-to-moderate AD cases. It improves cognitive functions and daily life activities. Oral administration of the drug is associated with adverse effects such as nausea, vomiting, dyspepsia, asthenia, anorexia, and weight loss. Initial dose 1.5 mg twice daily, increase to maximum dose 6 mg twice daily. Rivastigmine can be delivered by transdermal patches for controlled and continuous delivery of the drug through the

skin, with enhanced tolerability and caregiver satisfaction. Also, the patches can deliver a lower dosage compared to pills, which results in reduced side effects.

Galantamine (GAL) is considered a standard first-line drug for mild-to-moderate AD cases. It has a dual mechanism of action in which it acts as a competitive inhibitor of AChE and can bind allosterically to the α-subunit of nicotinic acetylcholine receptors and activate them causing ACh release. GAL can improve behavioral symptoms, daily life activities, and cognitive performance with good efficacy and tolerability, similar to other AChE inhibitors. Initial dose is 4 mg twice daily, increase on monthly basis to maximum dose to 16 mg/day. It is contraindicated in hepatic and renal impairment.

2. **N-methyl-D-aspartate (NMDA) antagonists:** Memantine is the only approved drug in this category to treat moderate-to-severe AD. Memantine is a low-affinity uncompetitive antagonist of the NMDA receptors in the brain and regulating activity of a subtype of glutamate receptor that prevents over-activation of the glutaminergic system involved in the neurotoxicity in AD cases. Memantine is used for the treatment of moderate-to-severe AD alone or in combination with AChEI. It is given along with donazepil for maximum benefit. Dose—5 mg OD first week, 5 mg BD second week, 10 mg morning, 5 mg evening third week, 10 mg BD fourth week.

Non-pharmacological treatment—if symptoms are not severe (a) assessment of clear precipitants, e.g. (suboptimal prompting, personal care or toileting), social interaction, activity, exercise; (b) use of specific drugs is based on psychiatric treatment in younger patients and avoiding drugs with marked anticholinergic property.

Other promising compounds called chaperones like heat shock proteins and vacuolar sorting protein 35 (VPS35) function by assisting other proteins to function normally and to arrive at their destination in the cell safely, and therefore can be used as a treatment for neurodegenerative diseases. The success of AD treatment depends on its early administration and patient monitoring for disease progression using biomarkers diagnosis. Future therapies that target tau pathology and the use of combination therapy may have a potential to slow the progression of AD pathology.

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Chapter 16

Management of Hypertension

Hypertension is leading cause of coronary artery disease, cerebrovascular disease, peripheral arterial diseases, aortic aneurysm, atrial fibrillation and end-stage renal disease. The treatment threshold as well as treatment targets are constantly updated according to guidelines of international societies based on emerging evidences from randomized-controlled trials. Major advances have been made in blood pressure recording methodology and unattended office blood pressure and ambulatory blood pressure monitoring are used to determine treatment threshold as well as targets. Such readings are more linearly related to hypertensive end-organ damage.

The goal of hypertension management is to prevent major adverse cardiac effects and to improve quality of life. As the goal of blood pressure management is to prevent cardiovascular complications, the treatment is individualized based on global cardiovascular risk of the patient. Lifestyle modifications are the first step in hypertension management. The three first-line drugs used in hypertension management include ACE inhibitor/ARB (angiotensin converting enzyme inhibitor/angiotensin receptor blocker), CCB (calcium channel blockers) and diuretics. Treatment is usually initiated with combination therapy of low dose ARB and CCB, and doses are up-titrated if blood pressure is not controlled. Diuretic is added to combination therapy if blood pressure is still not controlled. Resistant hypertension is treated with addition of mineralocorticoid receptor antagonist to full doses of ARB, CCB and diuretics as the most common cause of resistant hypertension is hyperaldosteronism. Statin is added to the treatment regimen if global risk of patient is high.

Joint National Committee (JNC) VII—Blood Pressure (BP) Classification (Table 16.1):

Table 16.1: Joint National Committee on prevention, detection, evaluation and treatment of high BP

Blood pressure classification	*SBP (mm Hg)*	*DBP (mm Hg)*
Normal	<120	<80
Pre-hypertension	120–139	80–89
Stage I hypertension	140–159	90–99
Stage II hypertension	≥160	≥100

PATHOGENESIS

The juxtaglomerular apparatus of the kidney secrete a proteolytic enzyme called renin. It is secreted in response to various physiological stimuli. Renin secretion is stimulated directly by renal sympathetic nervous system activity, β-adrenoceptor agonists and PGI2, whereas feedback inhibition is caused by angiotensin II (Fig. 16.1).

Atrial natriuretic peptide (ANP) also inhibits renin secretion. Renin is rapidly cleared from the plasma. It acts on angiotensinogen to split a decapeptide angiotensin I. Angiotensin I has no appreciable activity but is converted by ACE into angiotensin II which is a potent vasoconstrictor.

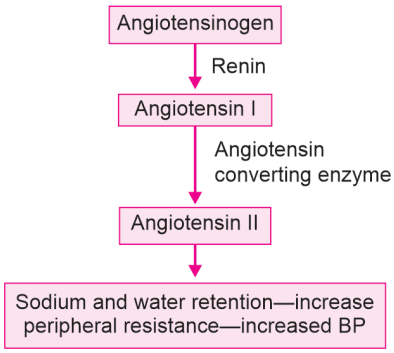

Fig. 16.1: Renin-angiotensin-aldosterone pathway

EXACERBATING FACTORS

- Obesity
- Increased salt intake, cigarette smoking, exercise
- Strenuous exercise may be deleterious, polycythemia
- NSAIDs, cyclophosphamide, low potassium intake
- The cause of primary essential hypertension is 90%. Secondary hypertension can be due to estrogen use, renal diseases—renal parenchymal disease, glomerular tubular interstitial disease, polycystic kidney, coarctation of aorta, hypertension associated with pregnancy, hypercalcemia, acromegaly, hyperthyroidism.

CLINICAL FEATURES

1. Asymptomatic
2. Symptomatic
   - Headache–suboccipital early morning pulsating headache, relieved during daytime.
   - Accelerated hypertension—confusion, excess sleepiness, blurred vision, nausea, vomiting.
   - Pheochromocytoma—episodic hypertension of anxiety, palpitation, perspiration, pallor, tremor.
   - Chronic hypertension due to underlying vascular diseases leading to cerebral ischemia, angina pectoris and dysnoea due to cardiac failure.
   - Cerebral involvement may lead to a stroke due to thrombosis.
   - The microaneurysms of small penetrating intracranial arteries may bleed and focal symptoms with dementia.
   - Nephrocalcinosis
   - Pain due to aortic dissection
   - Atherosclerotic complications

DIAGNOSIS

It is done by hematocrit studies, urine examination and kidney function tests to detect hematuria, proteinuria, casts. Blood glucose is also measured. It can rise due to diabetes associated with arteriosclerosis. Serum potassium and calcium are also checked. Uric acid is measured. It is raised in renal diseases. Serum lipid profile is also tested to identify factors predisposing to arteriosclerosis. Chest X-ray is done to detect pulmonary cause of

hypertension and ECG to detect cardiac status. Echocardiogram is a more specific test to detect secondary causes. Special studies are done to screen for secondary hypertension which include:

- Renovascular hypertension—detected by renal duplex ultrasound.
- Pheochromocytoma—detected by 24 hour urine assay for creatinine, catecholamines.
- Cushing's syndrome—is detected by suppression of cortisol by low doses of overnight dexamethasone.

MANAGEMENT OF HYPERTENSION

General measures are sufficient to control mild hypertension. Decreasing weight, restricting alcohol intake, smoking, taking low fat diet and low salt with increase in fruits, vegetables and fiber, relaxation therapy either used alone or in combination with other antihypertensives.

1. Diuretics

They cause sodium excretion along with loss of blood volume and ECF. They lower BP within 3–4 days, and provide adequate treatment for mild-to-moderate hypertension, e.g. hydrochlorothiazide 12.5–25 mg. Loop diuretics are used in hypertension only complicated by chronic renal failure, pulmonary edema, bilateral pedal edema due to hypoproteinemia. Furosemide does not work in BP >180 mm Hg. Potassium sparing diuretics—spironolactone in the dose of 25 mg, oral 2–4 times daily is used in hypertension due to hypermineralocorticoidism as adjunct to thiazide therapy and also used in renal failure patients. The complications associated with diuretics are hypokalemia, erectile dysfunction in males, carbohydrate intolerance, dyslipidemia, hyperuricemia, increased incidence of sudden cardiac death due to torsades de pointes.

2. Vasodilators

Decrease total peripheral resistance, increase venous pooling of capacitance vessels. They are used for mild-to-moderate hypertension. They are:

- **Hydralazine**—cause release of NO which causes relaxation of smooth muscle. Its peak effect is in 1 hour and antihypertensive action lasts for 6 hrs. It is used in combination with diuretic and β-blocker. Dose—25–50 mg OD-TDS.
- **Minoxidil:** Orally-acting vasodilator. It has longer duration of action and has more potency than hydralazine. The antihypertensive action after an oral dose lasts 12–24 hours. It is used for severe hypertension and resistant hypertension. Its side-effects are marked: Hair growth on face, body, fluid retention, coarsening of facial features. Dose—5 mg OD oral.
- **Diazoxide**—is used by IV route in hypertensive emergencies, lowers BP in 3–5 min after rapid IV injection, and produces direct relaxation of vascular smooth muscle. The dose is 3 mg/kg, IV, up to 150 mg rapidly. It causes hyperglycemia, hyperuricemia and sodium retention.

  Diazoxide and minoxidil activate K^+ channels in vascular smooth muscle leading to arteriolar dilation of blood vessels.
- **Nitrates:** They acts as vasodilators in heart failure, dilate arterioles by decreasing peripheral resistance–cause fall in BP. They activate soluble cGMP causing dilation of venules and arterioles. They are well-absorbed across skin and mucous membrane. They undergo first pass metabolism. Tolerance to vasodilator action causing headache comes and goes quickly. They are:
- **Sodium nitroprusside:** Dilates arteriolar and venous vessels. It is potent directly-acting vasodilator, indicated for hypertensive emergencies. Its action starts rapidly within 30 seconds after IV dose. Its dose is 0.25–1.5 μg/kg/min. Nausea, vomiting, headache may

occur which get resolved after discontinuation of infusion. Hypotension is a common side effect. If the rate of infusion is high >5 μg/kg/min or if infusion is given for longer period in patients with poor renal function, there is excess conversion of sodium nitroprusside to cyanide and thiocyanate.

3. ACE Inhibitors and Angiotensin II Antagonists

ACE inhibitors and ARBs cause vasodilation with little or no change in cardiac output. They are indicated in hypertension when excess renin production causes raised BP, e.g. renovascular hypertension. Over a period of weeks, the antihypertensive effect increases progressively with continued administration and increment in dose may be needed at intervals of 2 weeks. ACE inhibitors are captopril (2.5–150 mg), (enalapril, lisinopril, ramipril—2.5–5 mg). They inhibit the conversion of angiotensin I to II by inhibiting angiotensin-converting enzyme. Losartan (50 mg) and valsartan (80 mg), candesartan, irbesartan, telmisartan (40 mg) are all blockers of AT1 receptors. They have caused complete inhibition of angiotensin II action compared with ACE inhibitors. Also they are useful in patients with diabetic nephropathy as they reduce proteinuria and improve renal function. The adverse effects of ACE inhibitors are hyperkalemia, cough, rashes, urticaria, dysgeusia, fetopathic-growth retardation. In patients with bilateral renal artery stenosis, they dilate efferent arterioles and cause fall in glomerular filtration pressure, leading to acute renal failure. The advantages of ACE inhibitors over other antihypertensives are that they are free of postural hypotension, electrolyte imbalance, CNS effects, safe in asthmatics, diabetes, peripheral vascular disease, cause reversal of left ventricular hypertrophy and increased wall-to-lumen ratio of blood vessels that occurs in hypertension, minimum worsening of well-being, work performance, sleep and sexual performance.

4. Azilsartan

It is an angiotensin II receptor antagonist used in the treatment of hypertension. It is marketed as prodrug azilsartan medoxomil. The most common adverse effect in adults is diarrhoea. Dose is 40–80 mg, OD.

5. Alpha-blockers

Prazosin is more effective because it selectively blocks only postsynaptic alpha-1 adrenoceptors in arteriolar and venous vessels. The starting dose is low dose, 0.5 mg at bed time to prevent postural hypotension and fainting and the dose increased gradually for an adequate response. (max. 10 mg BD). Prazosin is suitable for diabetics, has favorable effect on lipid profile and improves symptoms in benign prostatic hypertrophy.

Phenoxybenzamine and phentolamine are administered in special situations—cheese reaction, pheochromocytoma and clonidine withdrawal, where catecholamines in circulation cause rise in BP (phenoxybenzamine 20–60 mg/day oral, phentolamine 5 mg IV). Prazosin is also used in Raynauld's disease and benign hypertrophy of prostate. It blocks α1-receptors in bladder trigone and prostatic smooth muscle facilitating urine flow. Terazosin oral 1 mg OD, doxazosin 1 mg OD, alfuzosin 2.5 mg BD, tamsulosin 0.2 mg, silodosin 4 mg OD, are also used in benign prostatic hyperplasia treatment.

5. Beta-blockers

The drugs block the effects of adrenaline (Ad) and noradrenaline (NA) and may be pure antagonists or partial agonists. The CVS effects of β-blockers result from blocking β-receptors,

decreasing sympathetic drive by reducing heart rate, reducing myocardial contractility and decreased rennin secretion from the JG apparatus in the renal cortex, e.g. atenolol 25–100 mg/day, nebivolol (2.5, 5 mg), more selective β1-blocker. They have vasodilator action by reducing cardiac output and peripheral vascular resistance. The dose of propranolol is 25, 50, 100 mg oral. They are used in lowering BP in mild-to-moderate hypertension. Metoprolol (25, 50 mg) inhibits stimulation of β_1-receptors, used in hypertensive patients who suffer from asthma, diabetes or peripheral vascular disease (PVD). Labetalol is used in cerebrovascular accidents (CVA) and in hypertension in pregnancy. The dose is 100 mg BD. It is used for moderating essential hypertension not responding to other β-blockers. β-blockers are contraindicated in bradycardia, hypotension and LVF.

7. Calcium Channel Blockers

Dilate peripheral arterioles and decrease BP, e.g. verapamil (5–10 mg shot), diltiazem, amlodipine (5–10 mg, once daily), felodipine, and nifedipine (5/2.5 mg sublingual). They are preferred in elderly hypertensive due to their high efficacy and excellent tolerability. But verapamil/diltiazem have negative inotropic/chronotropic action to worsen CHF and cardiac conduction defects.

8. Centrally-acting Hypotensive Drugs

They decrease cathecolamines release from the brain to the CVS system.

Alpha methyl dopa: It is converted into a methyl noradrenaline both at periphery and in CNS. In CNS, this metabolite acts as α_2-receptor agonist and mediates negative feedback inhibition of sympathetic outflow. It is used in cases when other drugs are not able to control BP in combination with diuretics. It is a safe drug to be used during pregnancy in the dose of 500 mg to 2 g, in 2–4 divided doses. It can be used by IV route also.

Clonidine: It acts as α_2 receptors agonist on α_2 presynaptic autoreceptors in the brainstem and decreases the central sympathetic outflow. It is well-absorbed orally, used in maintenance therapy in hypertensive emergency. The dose is 100 microgm TDS. It is used in maintenance therapy with β-blocker (metoprolol). Rebound hypertension is dangerous due to abrupt withdrawal of clonidine therapy. Dry mouth and sedation are frequent.

Treating hypertension: If the patient is young, use an ACE inhibitor or ARB. For older patients, give Ca channel blocker or thiazides. If BP is not controlled at 4 weeks, add a second line agent. If patient is on ACE inhibitor, add a Ca channel blocker or thiazide diuretic. Combining diuretic with ACE inhibitors is as good as the adverse metabolic effects of the thiazide will be ameliorated by the ACE inhibitors. If BP is not controlled by dual therapy, A + C + D is ideal triple regimen. If add on therapy is required, alpha blocker can be added at this stage. Resistant hypertensive patients who have aldosterone sensitive hypertension respond to spironolactone.

Salient Features of JNC-8 Guidelines

- Goal for all patients <60 years
  - BP should be <140/90 mm Hg, either presence or absence of diabetes (DM) or chronic kidney disease (CKD).
- Goal for elderly >60 years without CKD and DM
  - <150/90 mm Hg
- Goal for elderly >60 years with CKD or DM or both
  - <140/90 mm Hg.

Revisions in JNC-8 Guidelines

- **First-line drugs:** Thiazide, ACE inhibitors, ARBs and calcium channel blockers (CCBs).
- **Beta-blockers:** No longer considered as first-line drugs.
  - Due to increased mortality.

Precautions for hypertensive drugs:

- **ACE inhibitors or ARBs:** First choice drugs in patients with CKD irrespective of ethnic backgrounds.
  - ACE inhibitors and ARBs should not be given simultaneously.
- For African descent patients without CKD–CCBs or thiazides is preferred.

Pregnancy hypertension: Methyldopa and labetolol are safe drugs during pregnancy. For emergency reduction of BP in late pregnancy, parenteral hydralazine is reserve drug in combination with β-blockers (labetolol and atenolol). They are effective and are DOC in third trimester.

Treatment of hypertensive emergencies: The aim of treating hypertension is to decrease blood volume, decrease peripheral resistance and decrease cardiac activity. The emergency reduction of blood pressure is done in conditions like dissecting aneurysm, hypertensive encephalopathy, acute left ventricular failure. Malignant hypertension is characterized by marked BP elevation associated with papilloedema, retinal hemorrhages, headache, vomiting, convulsions, stupor, transient paralysis, coma. Diazoxide is easiest to administer in the dose of 50–150 µg IV and effect appears in 1–5 min. IV labetalol is particularly effective in severe hypertension due to pheochromocytoma and due to cheese reaction. In patients with MI, the best treatment is with β-blockers. Atenolol 25–50 mg, orally. In dissecting aneurysm continuous IV infusion of nitroprusside is used for treating. The dosage must be controlled with an infusion pump. Nitroglycerine is given by continuous infusion.

Hypertensive crisis—is sudden and excessive rise of arterial blood pressure to (250/150) with clinical and pathological manifestations. The patient should be admitted in hospital and given complete bed rest and tranquilisers like diazepam 5–10 mg three times a day.

Sodium nitroprusside: Infusion rapidly lowers BP. The dose is 0.3–10 µg/kg/min.

Glyceryltrinitrate—IV infusion 10–20 µg/min as it is a prominent vasodilator.

Fenoldopam—IV infusion at 0.1 µg/kg/min for short term control of severe hypertension. Contraindicated in glaucoma.

Clevidipine: 1–2 µg/kg/min

Diazoxide: Direct vasodilator as rapid IV dose of 100–150 mg repeated at 10 min.

Enalaprilat: It is an active ACE inhibitor used at dose of 0.625 mg to 1.25 mg every 6 hourly.

Nicardipine: 5–15 mg/hour IV but avoided in acute heart failure and cardiac ischemia.

β-blockers: Esmolol, ultrashort acting β-blocker given in loading dose 500 µg slow IV followed by maintenance dose 100–200 µg/kg/min. Its action lasts 20 min.

Furosemide: It helps other drugs to reduce BP by reducing circulating volume. 20–80 mg slow IV.

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Chapter
17

Treatment of Hyperlipidemia

Ischemic diseases related to cardiovascular and cerebrovascular system are responsible for causing morbidity and mortality in world over.

As the major cause for the development of ischemic diseases is related to dyslipidemia and resulting atherosclerosis, these are called atherosclerotic CVS diseases (Fig. 17.1). Disorders of metabolism of lipoproteins, including overproduction and deficiency of lipoproteins are classified as dyslipidemias. They may manifest as:

- Elevated total cholesterol levels
- Rise in LDL cholesterol levels
- Rise in triglyceride levels
- Lowering of high density cholesterol levels.

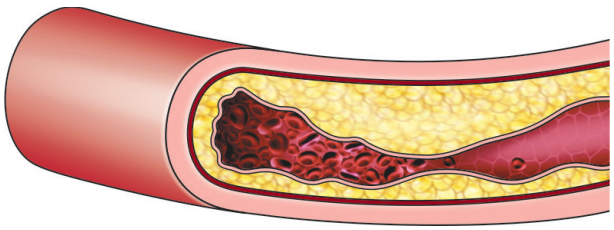

Fig. 17.1: Atherosclerosis

A number of genetic and acquired factors influence cholesterol metabolism resulting in hyperlipidemia.

Lipid transport and metabolism: Lipids after getting attached with several apoproteins, move in plasma in form of lipoproteins. The core of lipoprotein globules consists of triacylglycerols and cholesteryl esters. The outer polar layer is embedded with phospholipids, free cholesterol and apoproteins (Fig. 17.2). In decreasing order of atherogenesis, the clinically important lipoproteins are LDL, VLDL, chylomicrons and HDL. The CHD occurrence is linked with high total cholesterol and more strongly with elevated LDL. High levels of HDL decreases the risk of heart disease. The primary goal of cholesterol lowering therapy is reduction in LDL cholesterol.

Hyperlipidemia can be classified as:

1. Primary due to single gene defect–familial and called monogenic or genetic.
2. Secondary associated with diabetes, myxedema, nephritic syndrome, chronic alcoholism.

3. Multiple genetic, dietary and physical activity related causes—polygenic or multifactorial.

Foam cell ← ← Oxidiatively ruptured lipoproteins injury → → Endothelial injury

Smooth muscle injury

↓

Role of oxidized lipoproteins in altherogenesis

- Apoproteins are the surface proteins present on various lipoproteins. Their function is to provide structural stability to the lipoprotein and to determine its metabolic rate by transporting its lipid contents to various tissues and finally to liver. Apoprotein B48, synthesised in GIT and found in Chylomicron (CM) and CM remananth is responsible for their assembly and secretion. The absorption of dietary lipids occurs in the intestine with the help of bile acids. Chylomicrons are formed and passed into lacteals. They reach via thoracic duct into blood stream. While passing through capillaries, lipoprotein lipase bound to endothelium, hydrolyses the triglycerides into fatty acids. Fatty acids are taken up by muscle cells and utilised as energy source and taken by fat cells to be reconverted into triglycerides (TGs) and stored.

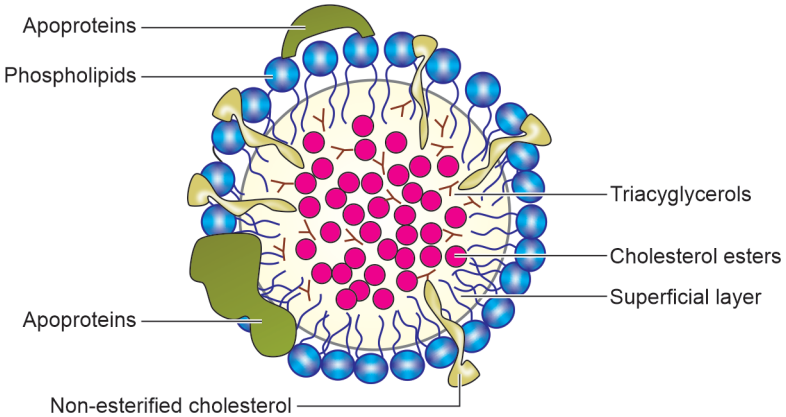

Fig. 17.2: Schematic structure of lipoproteins (SSL)

- B100, synthesised in liver and found in VLDL, IDL and LDL, is responsible to deliver lipids to artery wall, ultimately to liver.
- The chylomicron remanant composed of mainly CHE and little TG, is engulfed by liver cells, having receptors for surface apoproteins of chy rem. and digested.
- The liberated free CH is re-esterified and meets different fates—either stored in liver cells/released in blood or excreted in bile as CH/bile acids, after getting incorporated into different lipoprotein.
- Liver secretes VLDL containing mainly TGs and some CHE into blood. VLDL is acted upon by endothelium lipase. The remanant called IDL is taken back by liver cells while the rest becomes LDL containing only CHE. The LDL keeps circulating in plasma for a long time. The rate of LDL uptake is regulated by the rate of LDL receptor synthesis in a particular tissue.
- The CHE of LDL is used mainly for cell membrane function. The degradation of membranes releases cholesterol in blood that is rapidly incorporated in HDL. It is esterified with the

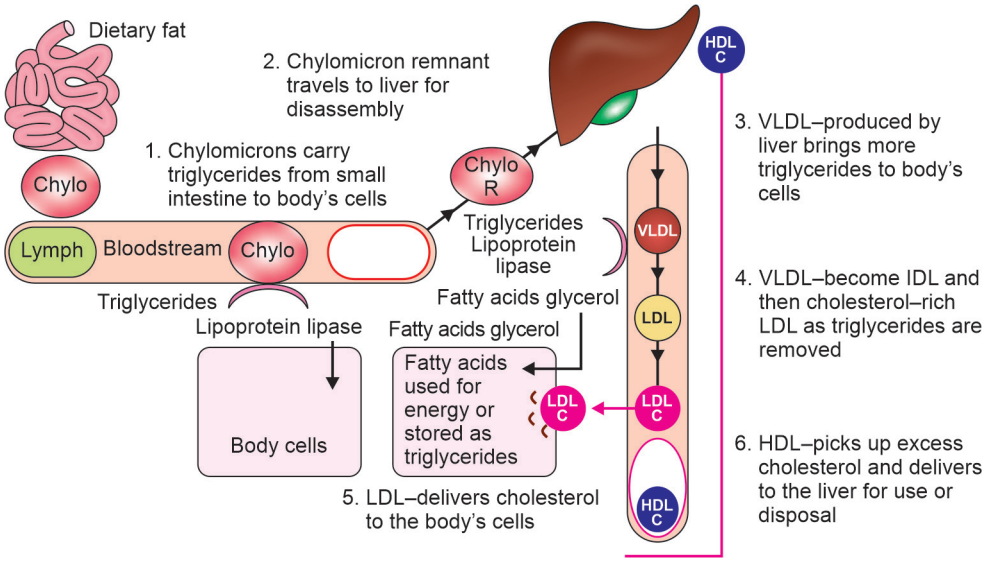

Fig. 17.3: Lipid transport and storage

help of an enzyme lecithin cholesterol acyltransferase and then transferred back to VLDL or IDL completing the cycle.

- The excess lipoproteins in plasma are disposed by macrophages. When too much of lipoproteins have to be degraded in this manner, CH is deposited in atheromas and xanthoma. Raised levels of VLDL, IDL and LDL cause atheromas while HDL may be protective as HDL helps in removal of CH from tissues (Fig. 17.3).

TYPES OF HYPERLIPOPROTEINEMIA

- Type I: Familial hyperchylomicronaemia—absence of lipoprotein lipase—triglycerides (TGs) in chylomicrons cannot be utilized, elevation in chylomicrons.
- Type IIa: Familial hypercholesterolemia—deficiency of LDL receptors, excess LDL.
- Type IIb: Familial dysbetalipoproteinemia—increased CH as well as TGs.
- Type III: Familial dysbetalipoproteinemia—remanants of VLDL and chylomicrons.
- Type IV: Familial hypertriglycerdemia—VLDL raised.
- Type V: VLDL and chylomicrons elevated.

Classification of Hypolipidemics

- HMG-CoA reductase inhibitors—lovastatin, simvastatin, pravastatin, atorvastatin, rosuvastatin, pitavastatin.
- Bile acid sequestrants—resins cholestyramine, colestipol
- Lipoprotein lipase activators (PPARα activators)—clofibrate, gemfibrozil, benzafibrate, fenofibrate)
- Lipolysis and triglyceride synthesis inhibitor: nicotinic acid
- Sterol absorption inhibitor: Ezetimibe

MANAGEMENT

Any medical disorder that may be causing hyperlipidemia, e.g. diabetes, hypothyroidism, hyperlipidemia, should be treated. Those who are overweight should reduce their total caloric intake and reduce fat intake.

- **HMG-CoA reductase inhibitors:** They inhibit the enzyme HMG-CoA reductase and competitively inhibit conversion of 3-hydroxy 3-glutaryl coenzyme A to mevalonate, a step in cholesterol synthesis. At therapeutic doses, they reduce CH synthesis by 20–50%. Also, there is compensatory increased expression of LDL receptors on liver cells. The receptors takeup LDL and catabolism of IDL and LDL occurs.
- There is difference among statins regarding their potency and efficacy in reducing LDL CH. The peak LDL-CH lowering occurs after 1–2 week therapy with all statins. They also cause concurrent fall by 10–30% in plasma TGs due to reduction of VLDL. A moderate rise in HDL-CH by 5–15% also occurs.
- All statins are administered at bed time to obtain maximum effectiveness because HMG-CoA reductase activity is maximum at midnight.
- Atorvastatin—dose—10–40 mg/day
- Rosuvastatin—is newer commonly used and more potent statin. 10 mg = 20 mg atorvastatin. It is used in severe hypercholesterolemia to obtain greater LDL-CH reduction.
- All statins are well tolerated drugs. Muscle aches are the commonest (10%) side effect. Monitoring of liver function is recommended as they raise serum transaminase. Myopathy and rhabdomyolyses may occur rarely. When nicotinic acid/gemfibrozil/CYP3A4 inhibitor are given concurrently, myopathy is more common.
- Statins are the first-choice drugs for primary hyperlipidemias with raised LDL and total CH levels with or without raised TG levels as well as for secondary hypercholesterolemia.
- **RESINS (cholestyramine and colestipol):** These anion exchange resins in the gut bind bile salts in intestine. The bile acids generally undergo enterohepatic circulation—movement of bile acid molecules from the liver to the intestine and back to the liver traverse the hepatocyte and actively secreted into canalicular bile. Resins interrupt this enterohepatic circulation by binding to bile salts. They increase hepatic conversion of cholesterol to bile acids increasing the fecal excretion of bile salts and cholesterol. Plasma LDL cholesterol falls by 20–25%. Resins are the safest hypolipidemic drugs. They are made into a paste before taking. The dose of cholestyramine is 4 g TDS or QID.

They are unpalatable and cause nausea, flatulence, heart burn, constipation, deficiency of fat soluble vitamins. Bile acid resins can also lead to hyperchloremic acidosis in children and patients with kidney failure. They decrease the absorption of orally administered drugs—digoxin, warfarin, thiazides, statins.

- Available bile acids in resins are cholestyramine, colestipol, colesevelam. These are drugs for type 11a, i.e. familial hypercholesterolemia and in type 11b hypercholesterolemia. they may be used along with niacin. Other uses include relieving of pruritis in patients suffering from cholestasis and bile salt accumulation. They are available in granular form to be taken orally.
- Adverse effects include constipation. Absorption of fat-soluble vitamins and of folic acid can be impaired. Because these resins bind to digitalis, they can be used in digitalis toxicity.

- **Fibrates:** The fibrates activate lipoprotein lipase enzyme involved in degradation of VLDL resulting in lowering of TGs. This action occurs through peroxisome proliferator activated receptor α. It is a gene transcription regulating receptor present in liver, fat and muscles. Activation of PPAR-alpha leads to: (a) increased expression of lipoprotein lipase located in vascular endothelium, (b) a decreased expression of ApoC111 to enhance lipoprotein lipase activity, (c) increased activity of ApoA1 which facilitates the reverse cholesterol transport to HDL. PPAR-alpha may also cause enhanced expression of LDL receptors in liver, fat and muscles. Fibrates decrease hepatic TG synthesis as well.
- Fibrates decrease TG levels by 20–50% along with 10–15% decrease in LDL and 10% increase in HDL. Gemfibrozil also reduces VLDL secretion by liver.
- *Fenofibrate*—It is fibric acid derivative possessing greater HDL CH-raising and greater LDL-CH lowering action than other fibrates. It is suitable drug as additive in subjects with raised LDL-CH levels and raised TG levels. Adverse effects are myalgia, hepatitis, rashes. Fenofibrate is recommended for combining with statins because it minimally affects statin metabolism and lowers enhancement of statin myopathy. Fenofibrate is uricosuric and is used when hyperuricemia coexists with hyperlipidemia. 200 mg OD with meals.
- *Gemfibrozil:* Lowers plasma TGs by enhancing breakdown and suppression of hepatic synthesis of TGs. Gemfibrozil is a first-line drug for patients with markedly raised TG levels. Episodes of acute pancreatitis are prevented in patients with chylomicronemia and severe hypertriglyceridemia. Adverse effects are skin rashes, bodyache, eosinophilia, impotence. Gemfibrozil and statin increase the risk of myopathy. 600 mg BD taken before meals.
- *Benzafibrate* is alternative to gemfibrozil in mixed hyperlipidemias type III, IV, V. It has greater LDL cholesterol lowering action than gemfibrozil. 200 mg TDS with meals

  Fibrates are well absorbed from GIT. The half-life of gemfibrozil and benzafibrate is short while that of fenofibrate is long.

  The fibrates are drugs of choice for treating familial hypertriglycerdemia (type IV) in order to prevent pancreatitis and dysbetalipoproteinemia. Type IIb hyperlipoproteinemia requires use of niacin with fibrates to lower both LDL and VLDL.

  The fibrate drugs lower VLDL by >40% and increase plasma HDL by >10%.
- **Nicotinic acid:** Niacin strongly inhibits lipolyses in adipose tissue thereby reducing production of free fatty acids. It reduces LDL levels by 10–20% and increases HDL-C. At doses of 1.5–3 g/day, it also lowers triglycerides by 20–35% Niacin can be used in combination with statins. Its mostly used to treat pancreatitis associated with severe hypertriglyceredemia, mostly in type IV and V disorders. The liver normally uses circulating free fatty acids as major precursor for TG synthesis. Reduced fatty acids lead to reduced liver triglycerides leading to decreased hepatic VLDL production, which in turn reduces LDL-C plasma concentrations.
- Since niacin lowers plasma levels of both cholesterol and triglycerides, it is useful in treatment of familial hyperlipidemias. It is also used to treat other severe hypercholesterolemias, often in combination with other agents.
- **Sterol absorption inhibitor:** Ezetimibe—it is a novel drug that acts by inhibiting absorption of cholesterol and phytosterols. It interferes with a specific CH transport

protein NPC1L1 present in the intestinal mucosa. Ezetimibe interferes with this protein and reduces absorption of both dietary and biliary cholesterol. It may be used in mild hypercholestrolemia when a statin is contraindicated. The combination of ezetimibe + low dose statin is as effective in lowering LDL-CH as high dose of statin alone. The dose is 10–20 mg.

SUMMARY

Raised plasma CH is leading cause of coronary artery disease. Whereas raised LDL-CH causes atherosclerotic disease, a higher HDL-CH level is protective or indicates a low atherogenic state.

- Lifestyle factors like exercising daily for half hour, low fat, low cholesterol diet, restricting saturated and transfats, cutting down excess bodyweight, stopping smoking, restriction of alcohol are primary approaches.
- The hypolipidemics are prescribed based on not only on LDL-CH level and the type of lipid abnormality but also on associated CAD risk factor or existing CAD.
- All subjects should receive statin therapy if LDL-CH is >190 mg/dl. The goal should be to titrate to achieve the goal LDL-CH level of 30% reduction. The standard statin therapy lowering LDL-CH by 30–40% reduces CVS events by 30–35% while intensive CH lowering by 50% curtails CVS events by nearly 50%.
- Statins are the primary drugs to lower LDL-CH. Statin therapy should be commenced at the dose estimated to attain targeted LDL-CH lowering. If the response is inadequate, dose should be doubled at 6 weeks interval or another drug should be added to achieve the target LDL-CH level.

Intensive lipid lowering by adequate dose of statin is considered to improve endothelial function, stabilize plaques in addition to antiatherosclerotic effect. All this leads to reduction in CAD, stroke and death.

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Chapter
18

Treatment of Angina and Myocardial Infarction

ANGINA PECTORIS

It is a ischemic heart disease characterized by paroxysmal attacks of substernal or precordial chest discomfort caused by myocardial ischemia. The pain may radiate to the left arm, shoulder or jaw. Angina pectoris involves tissue ischemia in which vasodilatory drugs are used. It is caused by an imbalance between the O_2 requirement of the heart and the O_2 supplied to it by coronary vessels. There are two types of angina pectoris:

Stable angina: It is known as typical angina characterized by chest discomfort on exertion and emotional stress. It is alleviated at rest or with nitroglycerine. It occurs to coronary artery occlusion due to atherosclerosis. It lasts for about 5 minutes.

Unstable angina: Occurs as a result of reversible coronary vasospasm called prinzmetal angina which occurs at rest. It lasts for 20 minutes or longer.

Pathophysiology: Three factors determine myocardial O_2 demand—heart rate, contractility and most important, intra-myocardial wall tension. An increase in heart rate, left ventricular preload and afterload increase oxygen demand. Left ventricular preload is increased by higher end-diastolic volume and left ventricular afterload increased by arterial stiffness, thus raising myocardial oxygen demand. The blood supply to the myocardium becomes compromised through atherosclerotic plaque or coronary artery spasm. Hence, the oxygen demand of the heart exceeds the supply leading to angina.

Principles of drug therapy: The pharmacotherapy of angina has two goals—to alleviate chest pain and improve quality of life and secondly to prevent CVS complications like myocardial infarction, arrythmias, heart failure. Nitrates relieve anginal symptoms raidly. β-blockers and calcium channel blockers are first line drugs for treating angina.

Classification of Drugs

Nitrates: They relax smooth muscles of arteries and veins, relieve coronary spasm, dilate epicardial coronary arteries and decrease myocardial O_2 demand. The sublingual route is preferred. Tolerance limits its long-term use. This can be prevented by giving nitrate free interval of 8–12 hours every day.

Following are nitrate group of drugs.

Isosorbide dinitrate, 5–10 mg: The oral bioavailability is very low. Sublingual nitrate bypasses the first pass metabolism and achieves a therapeutic effect rapidly. Duration of action—20–40 min.

Isosorbide mononitrate is used orally, 10–40 mg as its oral bioavailability is good. Duration of action—6–10 hrs.

Amylnitrite—is highly volatile liquid. When administered by inhalation route, provides rapid absorption due to bypass of hepatic first pass effect.

Nitroglycerine (glyceryltrinitrate) 0.5 mg causes relaxation of vascular smooth muscles increasing blood flow to the myocardium. It reduces venous capacitance and arterial resistance, decreases myocardial wall stress thus ameliorating anginal symptoms. It relieves angina within 5 minutes given sublingually.

Erythrityl tetranitrate and pentaerythritol tetranitrate: These are long-acting nitrates used for chronic prophylaxis of angina pectoris as pills or patches. Oral dose 10–40 mg.

β-blockers—decrease cardiac work, reduce myocardial O_2 requirement by decreasing the heart rate, prevent increase in sympathetic activity that increases O_2 requirement, that occurs due to stress or exertion.

Calcium channel blockers: All calcium channel blockers block the calcium channels in arterial smooth vessels and produce vasodilation. Amlodipine 5–10 mg OD, nimodipine 30–60 mg 6 hrly, felodipine, nitrendipine 10–20 mg OD, lacidipine 4 mg OD are orally active agents. They are avoided in acute attack as they precipitate reflux tachycardia. Nimodipine relaxes cerebral blood vessels and used in cerebral spasm of subarachnoid hemorrhage. 30–60 mg every 6 hrs. Calcium channels' inhibition in excess can cause serious cardiac depression including cardiac arrest, bradycardia, AV block and CHF.

In patients with variant angina, nitrates and calcium channel blockers are effective drugs for relieving and preventing ischemic episodes. They abolish anginal attacks in approximately 70% of patients. Unstable angina is treated with aspirin in dose range from 75–325 mg and IV heparin is indicated in most patients. Antiplatelet drugs–ticlopidine, clopidogrel-300 mg dose, gp11b. 111a antagonists have been found to be effective in decreasing risk in unstable patients.

Nicorandil: It causes activation of ATP sensitive K^+-channels leading to hyperpolarization of vascular smooth muscles, reducing calcium entry leading to muscle relaxation and vasodilation. It increases the conc of cGMP by donating NO group resulting in relaxation of vascular smooth muscle and vasodilation. It dilates both the epicardial and deep coronary blood vessels and increases blood flow to cardiac tissue. It also produces cardioprotective effect by facilitating recovery from ischemia in patients of MI. It is used as an alternative to nitrates when tolerance limits usefulness or in case of contraindications of other drugs in bronchial asthma and diabetes. It is useful in cases refractory to other drugs where surgery is indicated and used together with other drugs till surgery is performed. In case of MI, IV administration during angioplasty may improve outcome. Flushing, headache, dizziness and palpitation may occur. The dose is 5–20 mg BD.

Trimetazidine: It is inhibitor of fatty acid oxidation and is a metabolic modulator improving myocardial glucose utilization. It also reduces intracellular acidosis, reduces accumulation of sodium and calcium during myocardial ischemia and prevents O_2 free radical induced damage. It is used for long term treatment of angina and in post MI patients as an add on to first-line drugs. The dose is 20 mg TDS.

Ranolazine: It inhibits late sodium channel current in the myocardium and reduces calcium load and so the diastolic stiffness during myocardial ischemia reducing contractility and providing cardioprotection. It also inhibits fatty acid oxidation. Used alone or as addon, it reduces frequency of anginal attacks and prolongs exercise duration. It is effective for

refractory angina pectoris who are symptomatic on even first-line drugs. It also reduces incidence of ventricular arrythmias and AF in acute coronary syndrome (ACS) and Hb1AC in diabetic patients. It prolongs QT interval and avoided with drugs widening QT interval. The dose is 5 mg BD.

Ivabradine: It blocks pacemaker If current. This funny cation channel is mixed Na^+ K^+ inward current activated by hyperpolarization. The heart rate is reduced by reduced pacemaker activity and diastole is prolonged. These changes lead to reduction in demand for oxygen and increased blood flow to the myocardium. It is used in chronic stable angina in patients with normal sinus rhythm with HR >60/min. It reduces mortality when used with conventional drugs in heart failure. The dose is 5 mg BD.

Peripheral Arterial Disease

It is plaque formation in the arteries of legs or arms. The symptoms can range from asymptomatic to mild claudication (leg pain while walking), moderate-to-severe claudication to ischemic rest pain, worsening to form ulcers or gangrene.

Pentoxyphylline: The ischemic areas is perfused by reducing whole blood viscosity and by improving flexibility of RBCs. The rheological property rather than vasodilation improves passage of blood through microcirculation. The dose is 400 mg BD. Useful in peripheral vascular disease like deep vein thrombosis, Buerger's disease and Raynauld's phenomenon.

Cliostazol—is a PDEase inhibitor, increases cAMP in platelets and vascular smooth muscle causing antiaggregatory and vasodilatory effects. It is indicated for intermittent claudication in patients with no rest pain or heart failure. It is metabolized by CYP3A4 and CYP2C19 into metabolites. Dose is 100 mg BD, half an hour before meals.

MYOCARDIAL INFARCTION

Myocardial infraction results from long standing myocardial ischemia, precipitated in most cases by coronary thrombus occlusion at the site of pre-existing plaque. MI may also result from prolonged vasospasm or inadequate myocardial blood flow (Fig. 18.1).

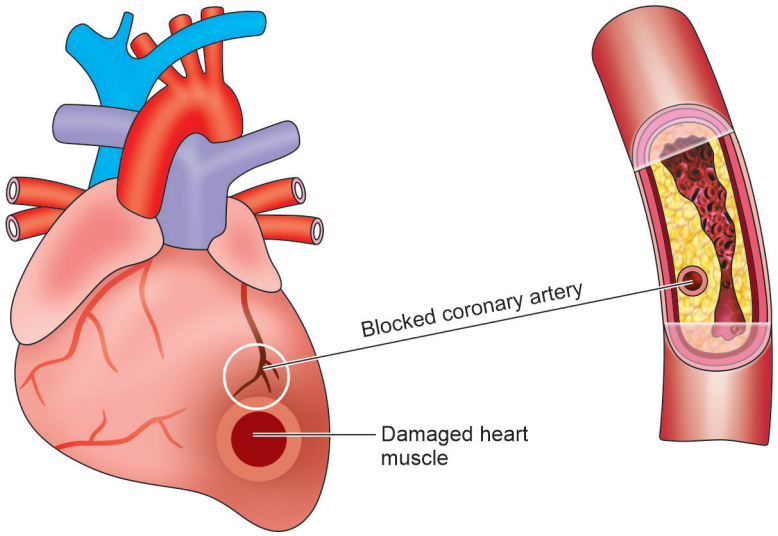

Fig. 18.1: Heart attack

MI is the commonest cause of death as a result of mechanical failure of the ventricle or from arrythmias which become unmanageable. About 25% die even before hospitalization. Myocardial cells survive on aerobic metabolism. If supply of O_2 to myocytes drops below a critical value, their necrosis and apoptosis results.

Acute Coronary Syndrome Classification

Unstable angina: Incomplete vascular obstruction, myocardial necrosis is absent, biochemical markers of ischemia are absent in blood and ST-segment is not elevated in ECG.

Non-ST-segment elevation MI: Incomplete vascular obstruction but there is a relatively small area of myocardial necrosis, biochemical markers are present in blood and ST-segment in ECG is not elevated.

ST-segment elevation MI: Complete vascular obstruction, larger area of myocardium is necrosed, biochemical markers—troponins-I and T and CK-MB, are prominent and ST segment in ECG is elevated.

A portion of the myocardium undergoes ischemic necrosis due to sudden occlusion of a branch of coronary artery due to an acute thrombus or vasospasm, leading to myocardial infarction. The specialized coronary care units take care with continuous monitoring of hemodynamic parameters, biochemical markers and ECG to guide the selection of drugs and dosage.

Drugs and other supportive measures like O_2 and fluids are used to prevent irreversible organ damage and complications following MI.

ACUTE MI TREATMENT

Prevention of thrombus extension, embolism, venous thrombosis: All diagnosed or patients with suspected MI patients should receive aspirin at the dose of 160 mg or 325 mg at once. Patients having allergy to aspirin may be treated with clopidogrel 75 mg daily orally. Anticoagulants-heparin followed by oral anticoagulants are used primarily to prevent deep vein thrombosis and pulmonary/systemic arterial embolism-heparin 5000 U every 12 hrs subcutaneous can be administered followed by oral anticoagulants on short term basis. Low molecular weight heparins, e.g. dalteparin or enoxaparin are now preferred.

Thrombolytic therapy and reperfusion—reduce mortality and limits infarct size in patients with acute MI. The golden rule is to treat within 1 and 1 and 1/2 hours so that a 50–60% reduction in mortality can be achieved. The benefits decline thereafter. Six fibrinolytic agents are available to achieve reperfusion of infracted area. Streptokinase is less clot specific, produces antigenicity. The infusion rate of streptokinase/reteplase is 100 ml in 500 ml NS in 1.5 hours @ 6–8 drops/min. It is given by IV infusion.

Alteplase has been obtained through recombinant DNA technique. It is thrombus specific. It has shorter half-life and shows high incidence of early reocclusion, thus necessitating concomitant use of IV heparin. It is infused over 90 minutes.

Tenecteplase is the only fibrinolytic agent injected IV as single bolus dose over 10 sec. It has higher fibrin selectivity, slower clearance from plasma and resists inhibition by plasminogen activator inhibitor-1 (PAI-1).

Urokinase is cheaper and is non-antigenic and does not produce hypotension. It is an enzyme prepared from cultured human kidney cells. It activates plasminogen directly. It is

used in patients of MI and for venous thrombosis and pulmonary embolism. It is given by slow IV injection. It causes fever during treatment.

Except for streptokinase, all preparations are very costly.

Thrombolytic therapy is contraindicated in (a) history of intracranial hemorrhage, (b) history of ischemic stroke in past 3 months, (c) history of head injury in past 3 months, (d) intracranial tumour/aneurysms, (e) history of bleeding disorders, (f) history of patient reciving anticoagulants, peptic ulcer, esophageal varices, (g) history of any wound or recent fracture or tooth extraction, (h) history of uncontrolled hypertension and (i) history of pregnancy.

Nitrates and vasodilators: Nitroglycerine is used for recurrent ischemia and lowers BP or relieves pulmonary congestion. Infused early, GTN limits infarct size and decreases mortality. Arteriolar, venous or a combined vasodilator such as nitroprusside can also be used.

Low O_2 therapy—2–4 L/min should be given if O_2 saturation is reduced and dysnoea occurs.

Maintenance of tissue perfusion and microcirculation: Slow IV infusion of saline/low molecular weight dextran is done.

Acidosis correction: Lactic acid production leads to acidosis, can be corrected by IV sodium bicarbonate infusion.

If accompanied by heart failure—dopamine or dobutamine inotropic drugs IV infusion may be needed to increase pumping action of heart. Oral digoxin 0.5 mg in 5 out of 7 days.

Tachyarrythmias can be treated with lignocaine or procainamide.

Sinus bradycardia with low cardiac output can be treated with atropine 0.5–1 mg IV.

β-blockers—like metoprolol—5 mg IV every 5 min for 3 doses in early stage of MI, reduces infarct size, prevents reinfarction, reduces duration of ischemia, incidence of ventricular fibrillation and chances of death. β-blockers should be avoided in patients whose heart rate is below 50/min, systolic BP is below 100 mm Hg and in those suffering from asthma, CHF or AV block.

β-blockers—metoprolol succinate, carvedilol, bisoprolol reduce the infarct size, lower the risk of reinfarction, CHF and mortality.

Control of hyperlipidemia—hypolipidemic drugs—atorvastatin 80 mg stat followed by 40 mg HS.

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Chapter
19

Treatment of Arrythmias

PHYSIOLOGY OF HEART

The cardiac cell is surrounded by lipoprotein membrane having receptor channels. There are ion-selective membrane spanning proteins that permit passive movement of ions—Na^+, K^+, Ca^{2+}, Cl^-. Na^+ channels are known as fast channels. Rapid depolarization is caused by Na^+ influx into cell. Sinoatrial (SA) and atrioventricular (AV) nodes depend upon movement of Ca^+ through slow Ca channels.

The drug action on heart can be understood by the following properties of heart.

1. Impulse generation—two types of myocardial fibres can be distinguished from electrophysiological point of view.
   Non-automatic fibers are ordinary working myocardial fibers having resting membrane potential (RMP) of –90 mV and of automatic SA node –60 mV. Though individual fibres are membranes bound, depolarization spreads radially through the syncytium due to presence of of gap junctions.

Rapid depolarization (phase 0) occurs due to sodium influx through rapidly opening sodium channels of single cardiac muscle fibre causing transmembrane action potential. Initial rapid repolarization (phase 1) occurs due to the inactivation of sodium channels. A plateau phase (phase 2) occurs due to calcium influx through more slowly-acting calcium channels. The sodium channels inactivation and a rapid repolarization process due to net movement of K^+ outside through K^+ channels is phase 3. That causes return to resting membrane potential phase 4 (Fig. 19.1).

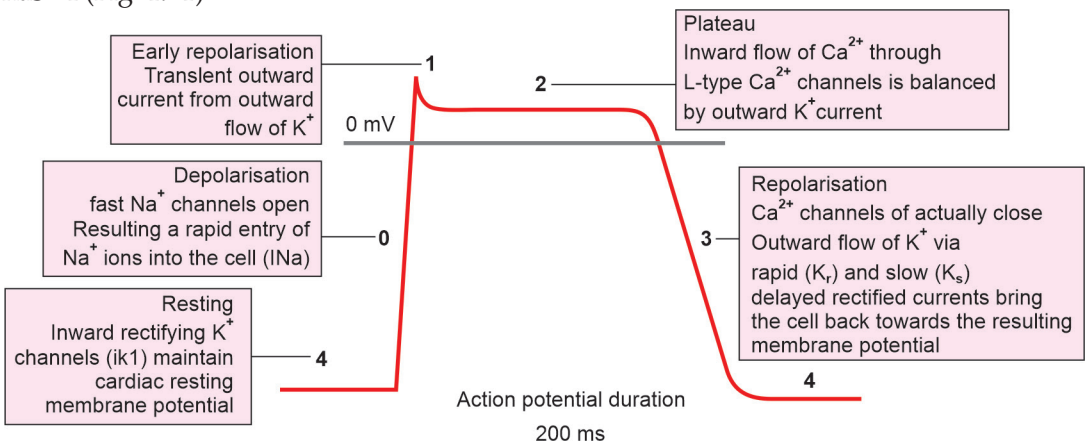

Fig. 19.1: Phases of the electrophysiology of heart

Automatic fibers: That discharge spontaneously are located in SA node and AV node and in His–Purkinje system. Also, patches of automatic tissue are there in the interatrial septum, AV ring and around openings of the great veins. The salient feature of these fibres is phase 4 or slow diastolic depolarisation, i.e. after getting repolarized to the maximum value, the membrane potential undergoes spontaneous decay, thus generating their own impulse. The action potentials (APs) in SA and AV nodes are largely due to calcium influx through transient and long-acting Ca channels. When transient channels open, they create the prepotential and when long channels open, they produce the impulse. Depolarisation starting from SA node spreads radially through atria, then travels to AV node. As conduction in AV node is slow, a delay of 0.01 sec occurs before the impulse spreads to the ventricle. The cardiac muscle has the properties as:

Conduction: The rate of conduction through a fibre is a function of its membrane responsiveness which is defined by rate of rise of action potential as a function of membrane potential at which activation occurs.

Excitability: The property of a fiber is defined by the strength of stimulus required to elicit a response or produce an action potential.

The **absolute refractory period** is the interval during which a second action potential absolutely cannot be initiated, no matter how large a stimulus is applied.

The **relative refractory period** is the interval immediately following during which initiation of a second action potential is inhibited but not impossible.

Pathophysiology of arrythmias: Cardiac arrythmias can arise due to ectopic focus of impulse, alteration of its rate or regularity or its conduction. Many factors or conditions—ischemia, hypoxia, acidosis/alkalosis, electrolyte abnormalities, pH imbalance, mechanical injury, stretching due to heart failure, neurogenic and drug influences including antiarrythmic drugs can worsen arrythmia by altering the electrophysiology of cardiac fibres like:

Abnormal automacity (less than 10%): The SA node is the pacemaker of the heart. If sites in cardiac tissue other than SA node start producing impulses on their own, they may generate competing stimuli and arrythmias may arise.

Abnormalities in impulse conduction (80–90%): Impulses from higher pacemaker centers travel along pathways that spread in two directions to activate the entire ventricular surface. A unidirectional block is caused by myocardial injury or prolonged refractory period causing abnormal conduction path leading to re-entry circuit. It is usually in diseased tissues causing a constant loop of APs re-exciting repeatedly (circus rhythm). The tissue starts beating independently of original stimulus. It can occur in atria, ventricles and nodal tissue.

Early after depolarisations (during phases 2, 3) and delayed after depolarisations (during phase 4) lead to abnormal pacemaker activity (Figs 19.2 and 19.3).

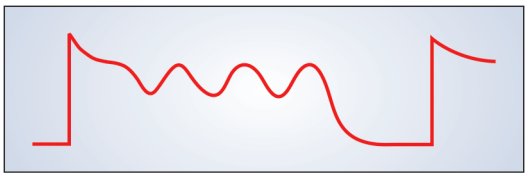

Fig. 19.2: Early after depolarizations

Due to reactivation of L-type calcium current

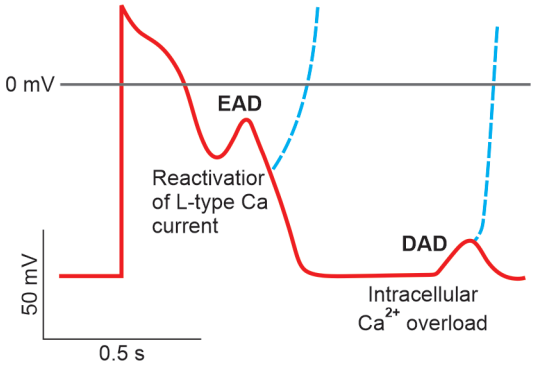

Fig. 19.3: Delayed after depolarisations

Classification of arrythmias from clinical perspective

- Heart rate (increased/decreased)
- Heart rhythm (regular/irregular)
- Site of origin (supraventricular/ventricular)
- Complexes on ECG (narrow/broad)

The important cardiac arrythmias are:

Extrasystoles are premature ectopic beats due to abnormal automacity or after depolarisations arising from an ectopic focus in the atrium, AV node or ventricle. The QRS complex in larger extrasystoles is broader and abnormal in shape (Fig. 19.4).

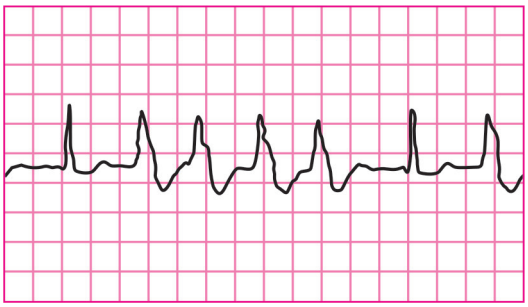

Fig. 19.4: Extrasystoles

Paroxysmal ventricular tachycardia (PSVT)—is sudden onset of atrial tachycardia (rate 150–200/min) with 1:1 AV conduction mostly due to circus movement type of re-entry occurring within or around the AV node or using an accessory pathway between atria and ventricle (Fig. 19.5).

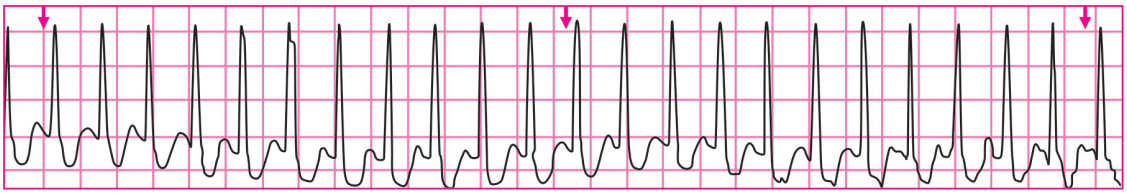

Fig. 19.5: Paroxysmal ventricular tachycardia

Ventricular tachycardia (VT)—is a run of 4 or more consecutive ventricular extrasystoles (Fig. 19.6)

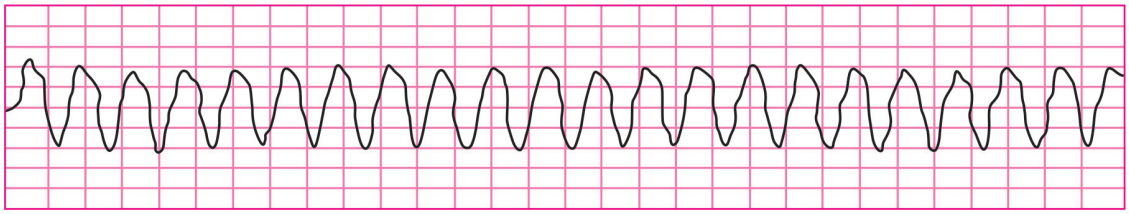

Fig. 19.6: Ventricular tachycardia

Ventricular fibrillation—is grossly irregular, rapid and fractionated activation of ventricles resulting in incoordinated contraction of its fibres with loss of pumping function (Fig. 19.7).

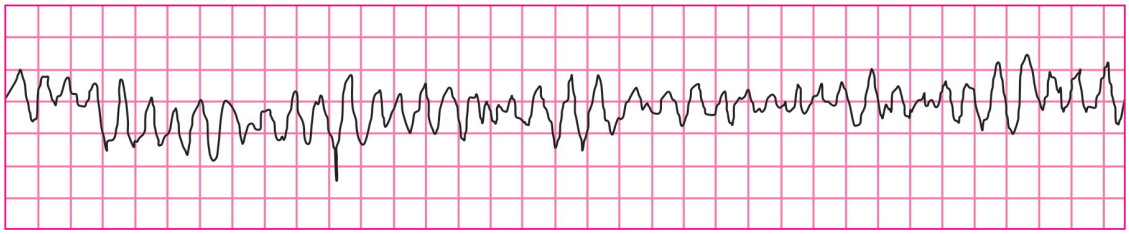

Fig. 19.7: Ventriucular fibrillation

Atrial flutter—beats at 200–350 beats/min and there is physiological 2:1 or 4:1 AV block.This is due to stable re-entrant circuit in right atrium (Fig. 19.8).

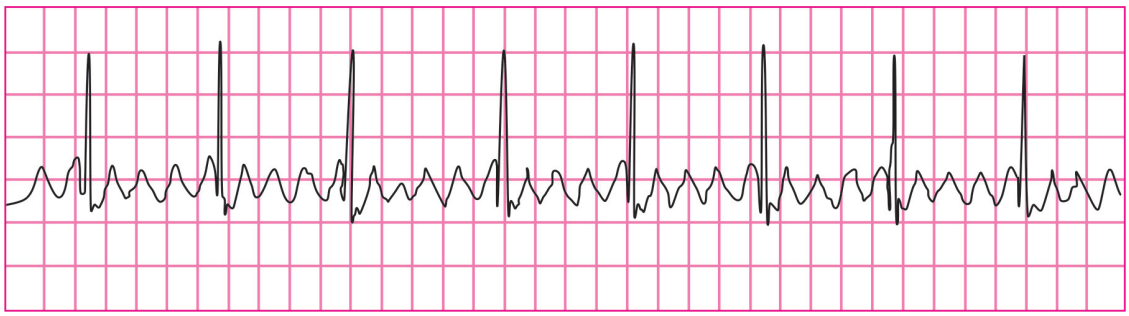

Fig. 19.8: Atrial flutter

Atrial fibrillation (AF) are activated asynchronously at the rate of 150–550 beats/min, associated with gross irregular and fast ventricular response (Fig. 19.9).

Fig. 19.9: Atrial fibrillation

Torsades de pointes—life-threatening form of polymorphic VT with rapid asynchronous QRS complexes and undulating baseline on ECG. An early afterdepolarisation can cause torsades de pointes (twisting of points) (Fig. 19.10).

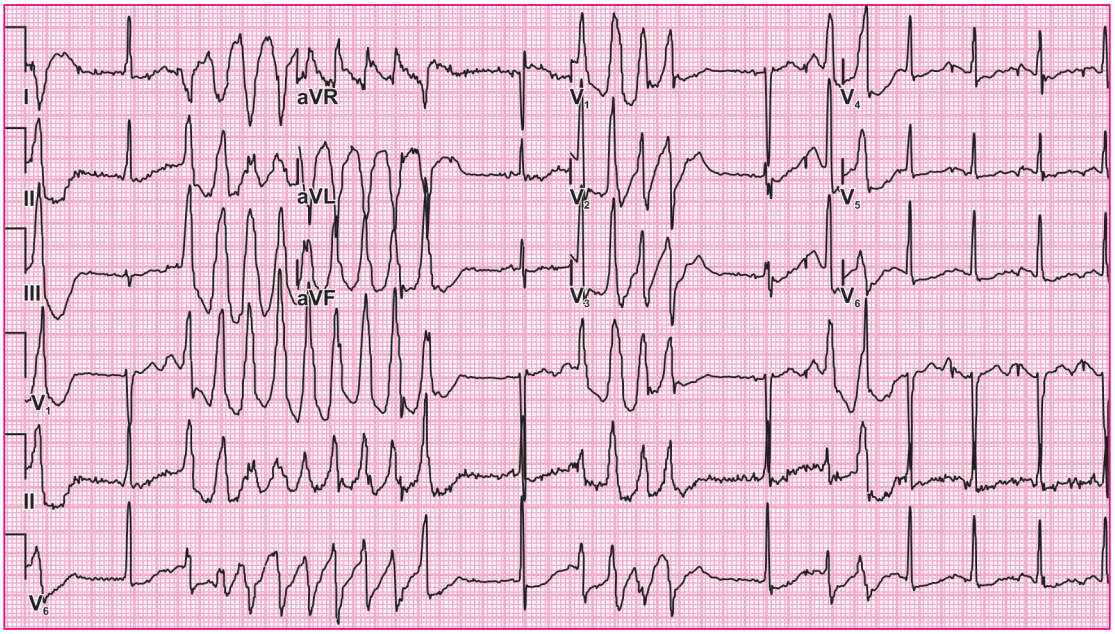

Fig. 19.10: Polymorphic VT

Atrioventricular (AV) block: Incomplete heart block (HB) is present, when the conduction between the atria and ventricles is slowed but not completely interrupted.

All the heart impulses reach the ventricles but the PR interval is abnormally long called **First degree HB**.

Second degree HB: A ventricular beat may follow every second or third atrial beat, QRS complexes are dropped as all the atrial impulses are not conducted to the ventricles.

Third degree HB: When there is complete interruption of conduction from atria to the ventricles, complete heart block ensues and the ventricles beat at a slower rate independently of the atria. The block is either due to diseased AV node or disease in the infranodal conduction system. The ventricles can beat at as low as 1/min in infranodal block, causing asystole to last minutes or so. The cerebral ischemia occurring as a result leads to dizziness and fainting. The third degree HB can be caused by septal MI and damage to bundle of His during surgery of ventricle septal defect (VSDs).

Signs of Arrhythmia (Figs 19.11 to 19.14)

These can be asymptomatic or feel like a skipped heartbeat (barely noticed).

May feel like a butterfly fluttering in the chest or neck.

Tachycardia can reduce cardiac output causing shortness of breath, chest pain, light-headedness or loss of consciousness.

Fig. 19.11: First degree heart block

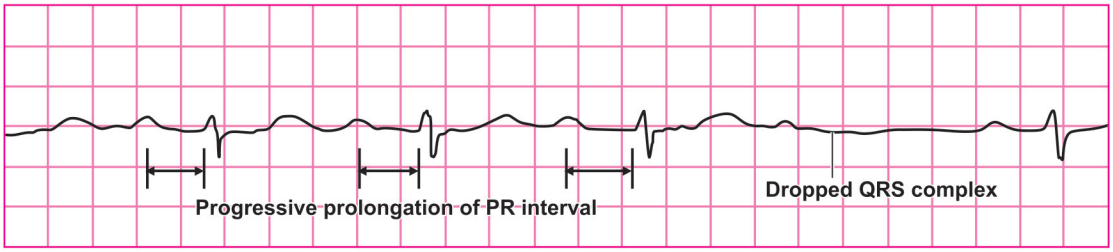

Fig. 19.11: Second degree heart block, type I (Wenckebach/Mobtz I)

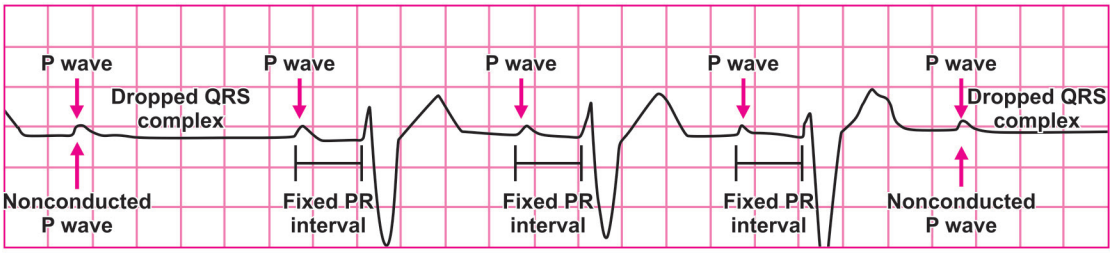

Fig. 19.13: Second degree heart block, type II (Mobtz II)

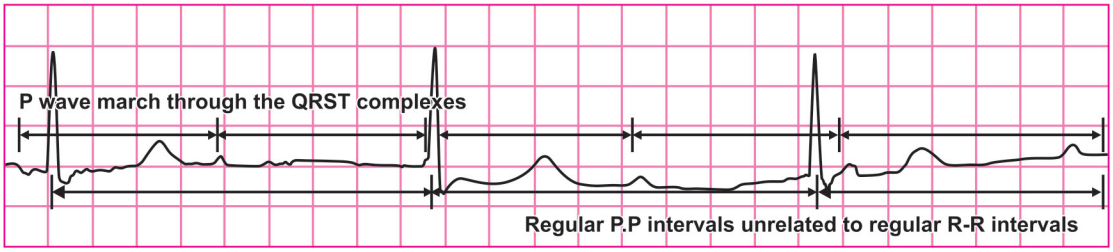

Fig. 19.14: Third degree heart block

If lasting for prolonged period, heart may not be able to pump enough blood >fatigue and lightheaded >may cause death.

Vaughan Williams' Classification of Antiarrhythmics

Class I: Sodium channel blockers are sub-divided into 3 categories:

- Ia: Prolong action potential, e.g. quinidine, disopyramide, and procainamide.

- Ib: Shorten action potential, e.g. lignocaine, and mexelitene.
- Ic: Minimal effect on action potential, e.g. flecainide, and propafenone.

Class II: β-blockers—sotalolol, and propanonol.

Class III: Prolong acion potential and refractory period, e.g. amiodarone.

Class IV: Ca channel blockers.

Class V: Digitalis

How are Arrhythmias Treated?

Find out its origin: An electrocardiogram (ECG), Holter monitor, exercise stress tests, tilt table test and electrophysiological studies.

Treatment includes:

- Lifestyle modification
- Pharmacotherapy to prevent and control arrhythmias
- Drugs to treat comorbidities such as high blood pressure, coronary artery disease and heart failure
- Anticoagulants to prevent development of blood clots and stroke episodes.
- A pacemaker implant for regularization of heart beat.
- AED-Automatic electronic defibrillator needed for synchronisation of heart rhythm, cardiac ablation and surgery.
- The major mechanisms are Na^+ channel blockade, blockade of sympathetic autonomic effects, prolongation of refractory period, Ca^+ channel blockade.

Antiarrhythmics are used to treat heart rhythm disorder. They bring heart rate to normal range and also decrease common symptoms—heart palpitation, irregular heartbeats, fast heart rate, light headedness, fainting, chest pain. The function of various channels that control transport of ions across cardiac cell membrane is altered. The conduction velocity, refractoriness and automaticity of cardiac tissue, based on which antiarrhythmics are classified, undergo changes.

Class I drugs—block sodium channels to varying degrees and also have variable effects on action potential duration.

Class Ia drugs—e.g. quinidine, procainamide, disopyramide slow conduction velocity and increase refractory period. Quinidine enhances contractility of the myocardium. It causes ventricular tachyarrythmias associated with QT prolongation, Torsades de pointes, cinchonism. Quinidine slows action potential upstroke and prolongs QRS. Its dose is 100–200 mg TDS. Disopyramide is effective in ventricular arrythmias, specially after MI. It is used orally 150 mg QID and well-absorbed. The antimuscarinic action leads to dry mouth, blurred vision, glaucoma and urinary retention. Procainamide is effective against most atrial and ventricular arrythmias. It is administered safely by IV and IM route and well-absorbed orally. Adverse effects are induction of torsades de pointes arrythmias and syncope. Dose—50 mg/kg/day IV.

Class 1b drugs—e.g. lidocaine, tocainide, mexiletene, and phenytoin actually have little effect on depolarization. They decrease action potential duration and shorten refractory periods when used by IV route. Lignocaine is used for ventrtcular arrythmias. 50–100 mg bolus followed by 20–40 mg every 10–20 min or 1–3 mg/min infusion. Its half-life is 2 hours. Mexiletene is used for ventricular arrythmias complicating MI. Dose of mexiletene is 100–200 mg slow IV. The oral dose is 150–200 mg TDS with meals.

Class Ic drugs (Flecainide, encainide, propafenone)—have a pronounced depressant effect on conduction velocity with little effect on refractory periods. Flecainide is used in AV tachycardia, paroxysmal atrial fibrillation, ventricular tachycardia. Its half-life is 14 hours which is prolonged in elderly, cardiac failure, renal impairment. Encainide is drug of choice for AV reentrant tachycardia. Flecainide is contraindicated in patients with sick sinus syndrome, with cardiac failure. Adverse effects are blurred vision, abdominal discomfort, paresthesia, dizziness, tremor. The dose of propafenone is 150–300 mg TDS.

Class II drugs—are β-blockers. These drugs have little direct action on action potential and work mainly by decreasing sympathetic tone, e.g. atenolol, metoprolol, nadolol, and propranolol. They affect mainly SA and AV nodes and act indirectly by blocking β-receptors, useful in non-sustained VT. Propranolol oral dose is 20–80 mg TDS. Esmolol—0.5 mg/kg IV in 1 min followed by 0.05–0.02 mg/kg /min, IV infusion. Sotalol—80–320 mg, BD oral. Propranolol or esmolol injected IV can terminate torsades de pointes. Esmolol given IV can control ventricular rate in (AF/AFl), also terminates supraventricular tachycardia. Sotalol is effective in polymorphic VT and for maintaining sinus rhythm in AF/AFl.

Class III drugs—these drugs act by inhibiting rapidly-activating component of delayed rectifier K^+ current, increase action potential duration, e.g. amiodarone, dronedarone, dofetilide, ibutilide. Intravenous amiodarone is used in the treatment of recurrent ventricular tachycardia. It is used in atrial and ventricular arrythmias. It is given by oral or IV route. Both arrythmias need loading doses. Amiodarone has very long half-life = 50 days. The oral dose of amiodarone oral 200 mg daily. There is no dose adjustment required in hepatorenal and cardiac dysfunctions. Thyroid function must be monitored before and during therapy.

Class IV—calcium channel blockers–diltiazem, verapamil. These drugs depress slow inward calcium current and prolong conduction and refractoriness particularly in SA and AV nodes. Both the drugs can be given IV for rapid control of ventricular rate in AF/AFl. Diltiazem is considered superior than verapamil because of easy titration to target heart rate, causes less hypotension or myocardial depression. Verapamil can control attacks of paroxysmal supraventricular tachycardia (PSVT). The dose of Verapamil is 40–120 mg TDS oral, diltiazem 30–90 mg TDS.

Class V—digitalis, digitoxin–affect SA and AV node by decreasing vagal tone. Digitalis increases effective refractory period of atria, AV nodes, bundle of His, ventricle. AV conduction is slowed. It is used for controlling ventricular rate in ventricular fibrillation, atrial flutter, PSVT.

Adenosine: IV bolus dose of 3 mg over 3 secs is used for treatment of supraventricular tachycardia. The dose is repeated every 1–2 min under ECG monitoring. Adenosine acts on adenosine receptors which shorten action potential duration, cause hyperpolarization and decrease automacity in atria, SA and AV nodes.

Magnesium: The mechanism is not clear. It is useful in recurrent episodes of torsades de pointes—magnesium sulfate 1–2 g IV over 15 min, useful in digitalis induced arrythmias with hypomagnesemia, quinidine-induced arrythmias.

Adverse effects—antiarrhythmics can induce dangerous fatal arrythmias-extrasystoles, ventricular tachycardia, sudden cardiac arrest. Drugs like H1 blockers—terfenadine, prokinetic–cisapride and macrolides are contraindicated with antiarrhythmics. During their use, toxicity should be observed for changes in QT interval , bradycardia, arrhythmia and hypokalemia.

Non-pharmacological Therapy for Arrythmias

For example, DC cardioversion, vagal manoueveres, external pacing, permanent pacemaker, radiofrequency ablation, implantable defibrillator.

Anticoagulants are recommended when atrial fibrillation is present for >48 hrs. It can consist of oral warfarin guided by INR ratio of 2–3 for at least 2–3 weeks after cardioversion. Rate control after cardioversion can be accomplished with verapamil, diltiazem or β blockers.

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Chapter
20

Treatment of Congestive Heart Failure

PATHOPHYSIOLOGY OF CONGESTIVE HEART FAILURE

Cardiac failure is present when the heart cannot provide all organs with the blood supply appropriate to demand. Congestive heart failure (CHF) can be defined as the pathophysiological state resulting from impaired cardiac function rendering the heart unable to maintain an output sufficient for the metabolic requirements of the tissues and organs of the body. CHF occurs either because of decreased myocardial capacity to contract or an excessive load imposed on the heart by arterial hypertension, valvular disease, or AV shunt. The failure may involve the right ventricle (cor pulmonale) but more commonly it involves the larger, thicker left ventricle or both ventricles. In systolic failure, stroke volume is reduced because ventricular contraction is weak. The ejection fraction falls from 65% to as low as 20%. The initial response to failure is hypertrophy of cardiac myocytes and thickening of the ventricular wall. called cardiac remodeling. The poor cardiac output leads to activation of the sympathetic nervous system and increased secretion of renin and aldosterone so sodium and water are retained. These responses are initially compensatory, but the failure worsens and the ventricles dilate in the long run. In diastolic failure, the ejection fraction is initially maintained but the elasticity of the myocardium is reduced so filling during diastole is reduced. This leads to inadequate stroke volume and the same cardiac remodeling and sodium and water retention occur in diastolic failure.

When a large AV fistula is present, in thyrotoxicosis and in thiamine deficiency, cardiac output may be elevated but still inadequate to meet the needs of the tissues (high output failure).

Compensated and Decompensated Heart Failure

The factors that increase the right atrial pressure can maintain the cardiac output to a normal level despite continued weakness of the heart itself. When a person is in compensated heart failure, any attempt to perform heavy exercise will cause immediate return of symptoms of acute failure because of inadequate pumping to sustain the exercise.

If the heart becomes severely damaged, no amount of compensation, either by sympathetic nervous reflexes or by fluid retention can make this weakened heart pump a normal cardiac output and return of normal renal function is not there. Fluid continues to be retained and the person develops progressively more and more edema and this state of events leads to death (decompensated HF). In decompensation, the right atrial pressure (RAP) first rises due to fluid retaining mechanisms. The cardiac output first rises as the RAP rises but there comes

a point, when the cardiac function declines. This decline is caused by the overstretch of the heart, edema of the heart muscle, unable to pump even moderate quantities of blood and failure completely and there is edema of lungs (increased blood flow in the lungs elevates the pulmonary capillary pressure and small amount of fluid transudates into lung tissue and alveoli), bubbling rales in lungs and dysnoea (Fig. 20.1).

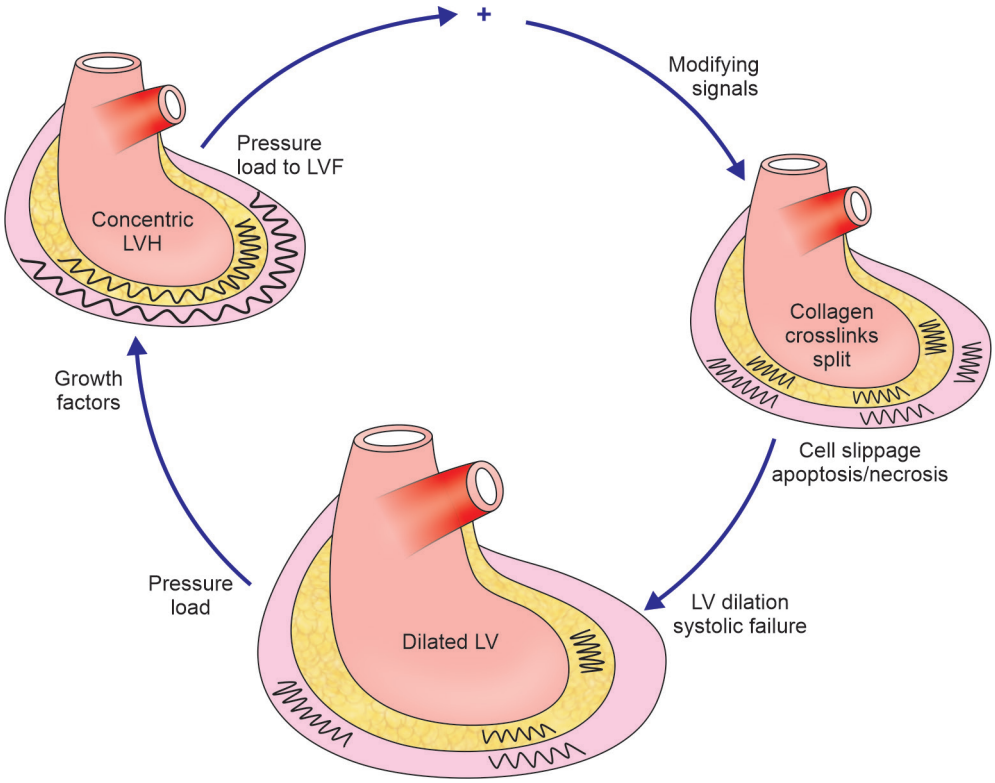

Fig. 20.1: Cardiac remodeling effect

The retention of fluid increases the mean systemic filling pressure, resulting in increased tendency for blood to return to the heart. There are three causes of reduced renal output of urine during cardiac failure.

1. Decreased glomerular filtration, even a slight decrease in GFR decreases urine output markedly.
2. Activation of the renin-angiotensin-aldosterone system (reduced blood flow to the kidneys cause marked increase in renin output).
3. Increased aldosterone secretion in response to rise in plasma K^+ due to reduced renal function.

Rationale of treatment: The 2 ways in which decompensation can be stopped: 1 by strengthening the heart by administration of a cardiotonic drug such as digitalis, 2 by administering diuretics and reducing salt and water intake to reduce fluid load.

Left heart failure—presents clinically as breathlessness, orthopnoea, paroxysmal nocturnal dysnoea.

Right heart failure—presents clinically as oedema, increased jugular venous pressure (JVP), hepatomegaly, pleural effusion (Fig. 20.2).

Echo—<50 left ventricular ejection fraction (LVEF)—ischemic heart disease.

Classification of Drugs

Management of cardiac failure requires both the treatment of any underlying condition and therapy directed at failure itself. Stroke volume is regulated by preload, afterload and contractility. The various treatment modes are:

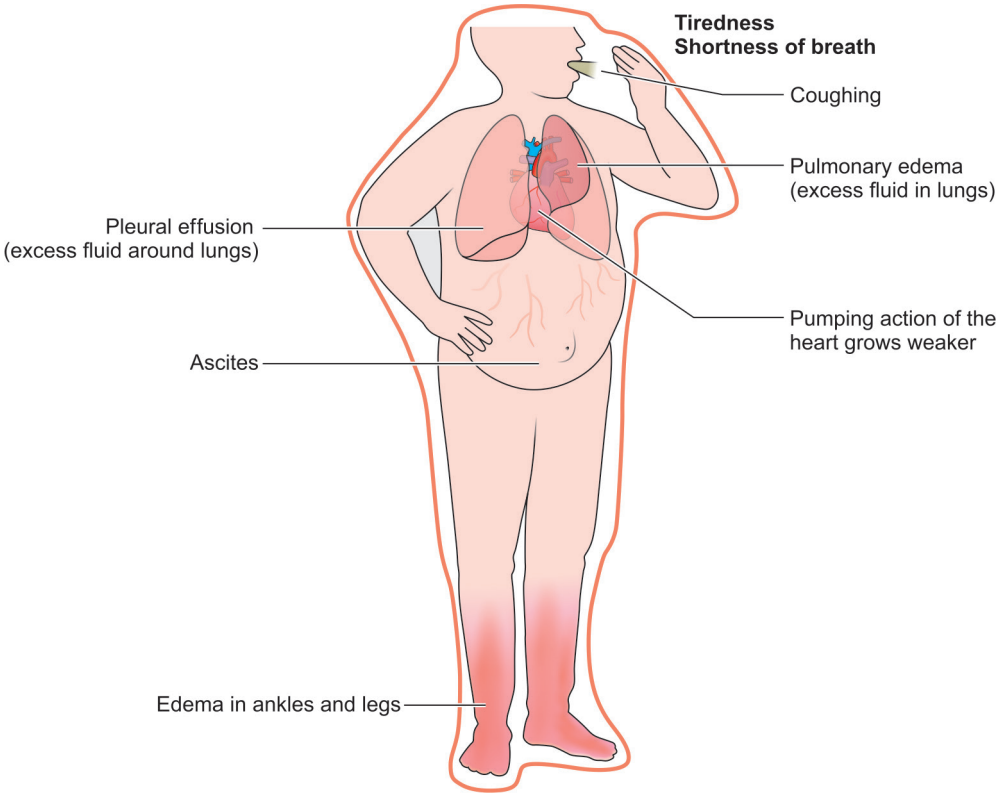

Fig. 20.2: Signs and symptoms of CHF

Diuretics: High ceiling diuretics (furosemide oral 40 mg OD/BD, bumetanide 1–10 mg/day) are diuretics of choice for mobilizing edema fluid. IV furosemide decreases systemic vascular capacitance and produces rapid symptomatic relief. Chronic diuretic therapy tends to cause hypokalemia, alkalosis, carbohydrate intolerance. Diuretics therapy improve congestive symptoms of cardiac failure which are due to increased filling pressure.

Vasodilators: Used IV to treat acute heart failure that occurs in advanced cases in MI and cardiogenic shock. They decrease:

Preload: Depending on whether predominant symptom is dysnoea; patient feels better, e.g. nitrates dilate capacitance vessels.

Afterload: Relaxes arteriolar smooth muscle and decrease peripheral vascular resistance. Hydralazine dilates arteriolar vessels. Initial dose 10–20 mg TDS, can be increased up to 100 mg TDS over days.

Pre and afterload reduction— Angiotensin-converting enzyme (ACE) inhibitors (captopril, enalapril), the starting dose is smaller (captopril 6.25 mg/lisinopril 5 mg/ramipril 5 mg sodium nitroprusside has high efficacy on 2 types of vessels.

Nitrates: Dilate smooth muscle in venous capacitance vessels and are also arterial dilators, decrease ventricular filling pressure and decrease myocardial O_2 requirement. Glyceryl trinitrate (GTN) given sublingual 0.3–1 mg for acute left ventricular failure (LVF) and repeated as necessary.

Isosorbide dinitrate—40–80 mg/day is given orally in divided doses.

β-blockers are used in mild-to-moderate CHF treated with standard ACE inhibitors and diuretic/digitalis. Starting dose should be low, then titrated upward as tolerated to target level.

Carvedilol 12.5, 25, 50 mg/day, metoprolol (10–20 mg), bisoprolol (1.25 mg–10 mg) and nebivolol (1.25–10 mg).

Spironolactone—is an add on therapy to ACE inhibitors and other drugs in moderate-to-severe heart failure. It causes antagonism of aldosterone induced-expansion of ECF volume, fibrotic changes in the myocardium, hypokalemia and hypomagnesemia. Spironolactone is contraindicated in renal insufficiency, causes hyperkalemia and gynecomastia.

Cardiac glycosides—are drugs having cardiac inotropic property. All are glycosides consist of aglycone to which are attached one or more sugar moeties. The pharmacological action resides in the aglycone but attached sugars modify the solubility and cell permeability. The pharmacological actions are:

Digitalis has direct effects on myocardial contractility and electrophysiological properties. It has vagomimetic action. Digitalis causes dose dependent increase in force of contraction of heart without proportionate increase in O_2 consumption. In addition, digitalis slows the heart by vagal and extra-vagal actions.

Mechanism of action: Increases force of contraction by direct action. It binds to Na^+ K^+ ATPase of myocardial fibres and inhibits the enzyme–progressive accumulation of Na^+ intracellularly–increased calcium intracellularly increased release of calcium from sarcoplasmic reticulum to case excitation contraction coupling.

Inhibition of Na^+ K^+ ATPase is involved in toxic reactions of digitalis.

Blood vessels: Systolic BP increases and diastolic may fall.

Kidney: It causes diuresis in congestive heart failure patients by improving circulation and renal perfusion.

CNS: High doses cause activation of chemoreceptor trigger zone (CTZ) activation—nausea, vomiting.

P. kinetics: Digitoxin is the most lipid soluble. Volume of distribution of cardiac glycosides is large, e.g. 6–8 L/kg in case of digoxin. All are concentrated in heart, skeletal muscle, liver and kidney.

Digitoxin is primarily metabolised in liver to digoxin and undergoes enterohepatic circulation. Digoxin is excreted unchanged by kidney. Its half-life is prolonged in elderly patients and in those with renal insufficiency. Cardiac glycosides are cumulative drugs. When maintenance doses are given from the beginning, steady therapeutic effects are attained after 4 half-lives.

All glycosides are irritant, cause pain and necrosis on IM injection. They get bound to muscle tissue. Parenteral route is utilized only in emergency.

All glycosides have same safety margin. Digoxin is well absorbed orally, has quick action, intermediate half-life, dose adjustments are possible in 2–3 days, can be used for routine treatment as well as emergency. Digitoxin may be used for maintenance.

Adverse Effects

Extracardiac: Anorexia, nausea, vomiting, abdominal pain. Cardiac: Every type of arrhythmia can be produced by digitalis.

Treatment: Further doses of digitalis can be stopped at the earliest sign of toxicity.

- For tachyarrhythmias, infuse KCl
- For ventricular arrythmias, lignocaine
- For supraventricular arrythmias, propranolol
- For AV block and bradycardia, atropine

Contraindications

- Hypokalemia
- Elderly, renal or severe hepatic disease
- Myocardial infarction
- Myxoedema/thyrotoxicosis
- Ventricular tachycardia
- Partial AV block
- Acute myocarditis

Drug Interactions

- Diuretics cause hypokalemia which can cause digitalis arrythmias.
- Calcium with digitalis precipitate toxicity.
- Quinidine increases digitalis toxicity by decreasing its binding to tissue proteins and its clearance.
- Hypokalemia, hypomagnesemia, increased calcium levels increase the toxic effects of digoxin causing arrythmias.
- Adrenergic drugs can induce arrythmias in digitalized patients.
- The plasma concentration of digoxin is increased in renal impairment, in elderly and in hypothyroidism due to reduced clearance.
- Verapamil, diltiazem, β-blockers-atenolol, spironolactone, itraconazole, cyclosporine increase serum digoxin concentration by competing with plasma protein binding.
- Metoclopramide decreases the absorption of digoxin and atropine increases the absorption.

Dosage

Slow digitalisation—in mild-to-moderate cases, maintenance dose of digoxin of 0.25 mg/day is given from the beginning. The dose for children is 2–20 mg/kg/min. Full response takes 5–7 days to develop. Relief of signs and symptoms of failure, reduction of heart rate and body weight to normal are the best guide for adequate response.

Phosphodiesterase III (PDE III) Inhibitors

Amrinone (selective phosphodiesterase III inhibitor)—it increases myocardial C-AMP and increases transmembrane influx of calcium. Its most important actions are on positive inotropic action and direct vasodilation.

In CHF patients, IV amrinone action starts in 5 min and lasts 2–3 hrs. It is indicated for short-term IV use in severe and refractory CHF. 5 mg/ml IV milrinone—more selective phosphodiesterase inhibitor with similar action 50 µg/kg IV bolus followed by 0.4–1 µg/kg/min infusion.

Sympathomimetic Inotropes

Dobutamine—is a selective β1-agonist with prominent inotropic action, used for acute heart failure accompanying MI, cardiac surgery as well as to tide over crisis in advanced decompensated CHF. The IV infusion rate is 2–8, µg/kg/min. It has the advantage of not increasing afterload.

Dopamine—improves renal perfusion and filtration rate by selective D1 agonistic action in refractory CHF who do not respond to diuretics. These inotropes are not used for long-term management because of cardiotoxicity and tolerance.

Other drugs

- Eplerenone 12.5–25 mg/day—is another aldosterone antagonist used for heart failure. It has less estrogenic side effect.
- **Neseritide**—brain natriuretic peptide is used IV short term to relieve dysnoea by increasing salt and water excretion and is potent vasodilator. 2 µg/kg IV followed by infusion .01 µg/kg/min.
- **Tolvaptan**—orally active vasopres sin V_2 receptor antagonist used for short term to correct water retention and hyponatremia in syndrome of inappropriate antidiuretic hormone secretion (SIADH) and in advanced CHF. Dose—7.5–15 mg/day.
- **Sacubitril–valsartan combination**—is used in advanced heart failure to increase survival rate. Sacubitril is neprilysin inhibitor given orally. It prevents degradation of vasodilator peptides causing vasodilation, natriuresis, and diuresis. Sacubitril 49 mg—valsartan 51 mg oral BD, initial dose. Maintenance dose—sacubitril 97 mg—valsartan 103 mg BD.

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Chapter
21

Treatment of Shock

PATHOPHYSIOLOGY OF SHOCK

Shock is a state of inadequate perfusion of the vital organs like brain, liver, kidney due to reduction in cardiac output. Initially, patient presents with weakness, fast heart rate, fast breathing, sweating, anxiety and increased thirst. Later as the shock worsens, there is confusion, unconsciousness or cardiac arrest. The diagnosis of shock is done by a combination of symptoms, physical examination and lab tests. The first change that occurs in shock is increased cardiac output followed by decrease in mixed venous O_2 saturation. The stages of shock are given below:

NON-PROGRESSIVE HEMORRHAGIC SHOCK

If the severity of shock is not great enough to progress on its own, the person eventually recovers. The compensatory mechanisms in shock involve the baroreceptor reflex that elicits powerful sympathetic stimulation of the heart, CNS ischemic response that drives more powerful sympathetic response on fall of arterial pressure below 50 mm Hg, formation of angiotensin and vasopressin, around the diminished blood volume—the contraction of blood vessels. The sympathetic reflexes provide help towards bringing recovery within 30 secs after hemorrhage. The rest mechanisms take 10 min to an hour. In addition, there occurs absorption of large quantities of fluid from the intestinal tract, fluid absorption from the interstitial spaces of the body, retention of water and salt by the kidneys and increased thirst and craving for salt, causing increased blood volume and takes 1–48 hrs.

PROGRESSIVE SHOCK

When there is fall in arterial pressure low enough, the coronary flow decreases to a level below that required for supplying the myocardium itself. Also decreased blood flow to the vasomotor center depresses the center and makes it passive. There is also thrombosis of the minute vessels due to sluggish blood flow and accumulation of acids due to tissue metabolism. The capillary permeability increases and ischemic tissues release toxins—fluid transudates into tissues thus decreasing the blood volume. The metabolic derangements lead to acidosis. At this stage of progression of shock, transfusion or any other therapy fails to save the life of a person, naming it as irreversible shock.

Types

Cardiogenic shock: After acute heart attacks in some instances, after prolonged periods of slow progressive cardiac deterioration, the heart fails to pump even the minimal amount of blood required to keep the body alive. Shock leads to low arterial pressure that reduces the coronary supply, which makes the heart weaker, making the shock still worse. All the body tissues begin to suffer and deteriorate leading to death within few hours to a few days. The need of the hour is to administer, inotropes like digitalis, give blood transfusion and administering vasopressors to increase the arterial pressure to cause rise in coronary flow. This prevents the vicious cycle of deterioration until compensatory mechanisms correct the shock.

Circulatory shock is a syndrome characterized by serious reduction of tissue perfusion due to inadequate cardiac output that can be—due to cardiac abnormalities that decrease the ability of the heart to pump blood and due to factors that decrease venous return. It leads to cellular and tissue hypoxia resulting in cellular death and vital organs dysfunction.

Hypovolemic shock: There is severe degree loss of plasma from the circulatory system leading to hypovolemic shock. There are many causes of hypovolemic shock. Intestinal obstruction, distension of the intestine causes fluid to leak from the intestinal capillaries into the intestinal walls and lumen. In patients with severe burns, damage to microvasculature causes rapid loss of plasma into the interstitium. Hypovolemic shock may occur because of excessive sweating, severe diarrhea, excess fluid loss by nephrotic kidneys, poor fluids and electrolytes intake, adrenal cortices destruction. Hypovolemic shock due to trauma occurs due to pain inhibiting the vasomotor center, increasing vascular capacitance and reducing venous return.

Neurogenic shock: There is sudden loss of vasomotor tone throughout the body causing massive dilation of the veins. The causes are deep general anesthesia, spinal anesthesia, brain contusion or concussion of the basal regions of the brain.

Anaphylactic shock is an allergic condition on exposure to an allergen, caused by release of histamine by basophils and mast cells due to antigen–antibody reaction. The cardiac output and arterial pressure often fall drastically. It is a life-threatening condition. Signs of anaphylaxis include itchy skin rash, swollen eyes, lips, hands and feet, feeling lightheaded or faint, swelling of mouth, throat or tongue causing breathing and swallowing difficulties, wheezing, abdominal pain, nausea, vomiting, collapse and unconsciousness.

Septic shock: The causes are peritonitis, generalized gangrenous infection, *Streptococcus* or *Staphylococcus* skin infection spread, colon bacilli spreading into blood from the kidney or urinary tract. Special features of shock are: High fever, marked vasodilation, high cardiac output, sludging of blood, developing of microclots in widespread areas of the body called disseminated intravascular coagulation (DIC).

Endotoxin shock: Occurs when a large segment of the gut becomes strangulated and loses much of its blood supply. The gut becomes gangrenous and bacteria in the gut multiply–colon bacilli–liberate endotoxin. On entering the circulation, endotoxin causes an effect similar to anaphylaxis resulting in severe shock. Also directly depresses the heart. Also, extension of urinary tract infections into blood causes septicemia.

Effects of shock: There occurs decreased metabolism and cellular deterioration in hypovolemic shock–decreased ability of the mitochondria to synthesize ATP, decreased ability of the cells metabolic pump to keep sodium low and potassium concentration high inside the cell. The cells' metabolic machinery caused depressed processing of nutrients by cells. There is rupture of many lysosomes releasing digestive enzymes within cells. Also, there is muscular weakness and low body temperature except in septic shock where the infection causes a temperature rise. As the shock progresses, mental haziness progresses to stupor and in late stages involuntary functions like vasomotor control and respiration fail. The renal function declines and renal deterioration leads to severe tubular necrosis.

TREATMENT OF SHOCK

The goals of treating shock are to correct the underlying cause and secondly in helping the physiological compensatory mechanisms to restore an adequate level of tissue perfusion. If blood loss is the primary cause of the shock as in hemolytic disorders, trauma, the treatment includes early and rapid transfusion of adequate amounts of compatible whole blood. In shock due to burns, there is lot of plasma loss causing hemoconcentration. Here, plasma is administered for burn shock resuscitation as it stabilizes the endothelium. Concentrated human albumin and other hypertonic solutions expand the blood volume by drawing fluid out of the interstitial spaces. So, used in septic shock who develop severe kidney injury. Appropriate electrolyte solution by IV infusion like Ringer's lactate, normal saline or dextrose solution can correct the shock in dehydration. A sympathomimetic drug is given—norepinephrine or epinephrine is used in neurogenic shock (activate the depressed sympathetic activity) and anaphylactic shock (oppose the vasodilating effect of histamine). They are not very valuable in hemorrhagic shock as the sympathetic system is activated by circulatory reflexes.

Management

The following measures should be carried out in all patients with shock.

A. General Treatment/First Aid

1. The patient's head must be kept at low position so that the right ventricle filling pressure is increased to raise the cardiac output. Elevate the legs and feet slightly.
2. Airway should be maintained by placing oropharyngeal airway over the tongue and if required endotracheal intubation is done.
3. IV fluids—blood in case of hemorrhagic shock, plasma or saline in burns, dextran in cardiogenic shock. Transfusion of fluids should be slowed down when central venous pressure is about 5 cm above the sternal angle.
4. Morphine 10–15 mg IM is given to relieve pain and anxiety.
5. Metabolic acidosis should be treated with 50–100 cc of 7.5% sodium bicarbonate IV.

B. Specific Treatment

Vasopressors have positive inotropic effect and peripheral vasoconstricting action. They are useful in cardiogenic shock due to myocardial infarction or arrythmias. Dopamine 500 µg in 500 ml of dextrose is given slowly through microdrip to ensure 5–15 µg/kg/min. It causes increase in cardiac output and blood pressure by acting on both alpha and beta-receptors.

Dobutamine given in the dose of 2–30 µg/kg/min acts on beta-receptors and improves cardiac output. Noradrenaline 2–4 mg in 500 ml of dextrose at the rate of 1–25 µg/min is required. 100–500 mg of hydrocortisone hemisuccinate is given immediately intravenously. It is useful in anaphylactic, cardiogenic, septic and neurogenic shock and in adrenal crisis.

Higher antibiotics like gentamycin 80 mg 8 hourly IM with third generation cephalosporins like ceftazidime 1 g 6 hourly and metronidazole 500 mg 8 hourly are useful in Gram negative septicemia. Cloxacillin is useful if staphylococcal infection is present.

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Chapter 22

Hemopoietic Agents and Treatment of Anemia

HEMOPOIETIC AGENTS

The hemopoietic machinery is primarily involved in the formation of cellular components of blood—erythrocyes, leucocytes and thrombocytes. For its organised functioning, it needs some essential exogenous nutrients such as iron, vitamin B_{12} and folic acid called hematinics and certain endogenous derived growth factors such as granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulatimg factor, erythropoietin, thrombopoietin, interleukin 1 and 11. Accessory vitamins include vitamins and minerals like copper, cobalt and manganese.

Anemia means a decrease in O_2 carrying capacity of blood due to reduced concentration of hemoglobin (Hb) of RBCs. The anemia occurs when the balance between production and destruction of RBCs is disturbed by: (a) blood loss, (b) deficiency of essential factors, i.e. iron, vitamin B_{12}, folic acid, (c) bone marrow depression, (d) erythropoietin deficiency and (e) increased destruction of RBCs.

Clinical Features

A patient with mild anemia complaints of fatigue, weakness and is pale. More severe anemic patients may suffer from faintness, dizziness, increased thirst, sweating, a weak and rapid pulse and rapid breathing. Also there can be painful lower leg cramps during exercise, shortness of breath and chest pain.

The anemia may be characterised as:

Microcytic hypochromic anemia—characterised by small RBC size with low Hb content, usually caused by iron deficiency.

Macrocytic anemia or megaloblastic anemia—characterised by large nucleated RBCs with increasingly pigmented blood smear, caused due to deficiency of vitamin B_{12} or folic acid.

Perinicious anemia—is megaloblastic anemia due to failure of secretion of intrinsic factor by the stomach.

Hemolytic anemia—is due to increased destruction of RBCs.

Aplastic anemia—results due to hypoplasia of bone marrow due to cytotoxic drugs or bone marrow disease, is associated with thrombocytopenia and neutropenia.

Sickle cell anemia—is type of hemolytic disease characterised by the presence of HbS in RBCs.

Sideroblastic anemia—is due to sideroblasts in bone marrow due to inadequate utilisation of iron.

Iron Deficiency Anemia

Hemoglobin is the oxygen carrying component of RBCs. It is made of haem + globin. Haem consists of ferrous iron chelated between porphyrin rings and the globin chain conjugated to this complex. When iron is inadequate, small erythrocytes with insufficient Hb are formed giving rise to microcytic hypochromic anemia. The clinical features include pallor, fatigue, dizziness, exertional dysnoea, and general symptoms of tissue ischemia.

Iron deficiency can result due to dietary deficiency, faulty absorption, transport and storage, excessive blood loss due to hemorrhage or heavy worm infestation, excessive demand during growth, pregnancy and lactation and during severe infection.

Total body content of iron is 3.5–4 g in adult male and 2.5 g in adult female, 70% of which circulates in the blood as Hb. About 15% is stored in liver, spleen and bone marrow as ferritin and hemosiderin. Ferritin is also present in intestinal mucosa. It is composed of a nucleus of ferric hydroxide with a protein envelope of apoferritin. Hemosiderin consists of aggregated ferritin crystals.

Liver, egg yolk, meat, chicken, fish are good sources of iron—pulses, dry fruits, spinach, banana, apple and wheat grains are moderate sources of iron.

Pharmacokinetics of iron: Maximum iron absorption occurs in the duodenum and proximal jejunum. Ascorbic acid, succinic acid and SH group containing amino acids facilitate conversion of ferric to ferrous form. Iron absorption is hindered by coffee, tea, antacids, phosphates. Iron is absorbed by active transport across intestinal mucosa where it is converted intracellularly from Fe^{2+} to Fe^{3+} iron. If the body does not need iron, the ingested iron gets bound to apoferritin to form ferritin, which is stored in all cells of the body and provides an efficient mechanism for iron storage and release on demand.

On body's demand for iron, transferrin enters the plasma and bind with free Fe^{3+} and carries it to bone marrow for being used in Hb synthesis. Some Fe^{3+} is stored as ferritin or as hemosiderin in reticuloendothelial cells and some in myoglobin, cytochromes and enzymes. Hemosiderin granules are seen with prolonged iron overload states.

Iron is well-conserved in the body. The major elimination is in faeces by exfoliation of GIT cells. Menstruation causes iron loss to 1–2 mg/day. Very small amount of iron is excreted through urine and sweat and due to desquamation of skin. Loss of iron also occurs during menstruation and delivery. Iron is also secreted into milk during lactation.

Clinical Uses

1. Iron deficiency anemia leads to microcytic hypochromic anemia [low mean corpuscular volume (MCV) and low mean corpuscular hemoglobin concentration (MCHC)]. It is recommended to find out the cause of anemia and treat the cause, e.g. peptic ulcer or hookworm infestation.
2. Prevention of iron deficiency during pregnancy, lactation and due to loss of blood during delivery. Iron should be administered starting from second trimester and continued till lactation. Iron supplementation may be required during infancy, in menstruating women and in blood donors.
3. Megaloblastic anemia—iron is required when rapid hemopoiesis occurs due to administration of B_{12} or folic acid.
4. With erythropoietin—iron is also used together with erythropoietin to produce adequate iron level.

Oral iron is as good and efficacious as parenteral. Iron preparations are available as ferrous salts—sulfate, fumarate, lactate, succinate and glycine sulfate. The most commonly used iron preparation is ferrous sulfate. Lately iron polysaccharide complex, carbonyl iron complex and ferric hydroxide–polymaltose complex have been marketed. A total of 200 mg elemental iron should be administered daily for 2 months after meals. In dialysis patients, ferric carboxymaltose is given.

All iron preparations have 100% iron content, least risk of overdose toxicity and better GI tolerance. Common complaint is constipation.

Parenteral therapy is used when oral administration fails, e.g. poor oral compliance, severe intolerance, malabsorption and in patients on total parenteral nutrition and patients with severe renal disease who are on dialyses and receiving erythropoietin. Parenteral iron is reserved for those who are unable to tolerate oral iron or for those with Hb <7 g/dl with acute or chronic blood loss (over 1 hour) or GIT disorders like sprue or inflammatory bowel disease.

Iron requirement for parenteral route—4.4 × body weight × Hb deficit.

Parenteral Iron Preparations

- Low molecular weight dextran up to 1500 mg. Ferric gluconate 125 mg per injection.
- Iron sorbitol citric acid 75 mg IM daily or on alternate days.
- Ferrous sucrose 100 mg IV injection over 5 minutes, once daily to once weekly. This preparation is used for anemia in kidney disease.
- Ferrric carboxymaltose daily 100 mg IV injection or up to 1000 mg with 100 ml saline. It is used in dialysis patients.

Parenteral Iron is Used in Two Ways

Either the total dose of iron is administered to correct the Hb deficit to replenish depleted iron stores.

The other way is common in dialysis centres where 100 mg of elemental iron is given weekly for 10 weeks to augment the response to erythropoietin therapy.

Symptoms after several days after infusion of a large dose of iron include arthralgia, skin rash and low grade fever.

The total calculated dose is diluted in 500 ml of glucose/saline solution and infused IV over 6–8 hrs under constant observation.

Acute iron toxicity is common in children and occurs on acute injection of large doses usually accidental. Treatment is by general supportive measures and diazepam, if there are convulsions. Emesis and gastric lavage with sodium bicarbonate and instillation of desferrioxamine 50 mg/kg by IM route or 20 mg/kg IV is done.

Hemopoietic Growth Factors

These are responsible to maintain a balance between proliferation and differentiation of various type of blood cells.

Erythropoietin is a cytokine produced in juxtaglomerular cells in the kidney and also in the macrophages. It is also produced by recombinant DNA technology. The dose of erythropoietin is 5000 U once weekly × 3–5 months for dialysis patients. Darbepoietin is a longer acting glycosylated form of epoietin, administered weekly. It stimulates erythrocyte

proliferation and differentiation. Can be used 100U/kg SC or IV in anemia resulting from cancer chemotherapy, anemia of AIDs by zidovudine treatment, in anemia of premature infants, to increase benefits of autologous blood transfusion.

Folic acid: Folic acid deficiency results in megaloblastic anemia because of impaired production of purines and pyrimidines which are essential for DNA synthesis. Also, it prevents development of fetal neural tube defects, e.g. spina bifida. The dose is 5 mg/day for 4 months given in pregnancy. Folic acid deficiency is associated with cancer, leukemia, myeloproliferative disorders, certain chronic skin disorders, spina bifida in the offspring. A dose of 2 mg of folic acid orally daily is sufficient to reverse megaloblastic anemia. The Hb level should begin to rise within the first week and the anemia should be completely corrected in 1–2 weeks.

Vitamin B_{12}: Cyanocobalamin and hydroxycobalamin are complex cobalt containing compounds present in the diet. Vitamin B_{12} is essential for correction for conversion of homocysteine to methionine. It affects purine and pyrimidine synthesis and DNA production. Demyelination and neurologic damage is seen in vitamin B_{12} deficiency. Hydroxycobalamin 1 mg IM/s.c is injected daily for 2 weeks followed by 1 mg injected every 2 months for maintenance in megaloblastic anemia. The symptomatic improvement starts in 2 days and complete blood count (CBC) restores in 2–3 weeks.

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Chapter
23

Treatment of Bleeding Disorders

HEMOSTASIS

It is the process of balancing the formation of blood clots in the walls of damaged blood vessels as well as preventing blood loss while maintaining fluidity of blood within the vasculature. There are interrelated systematic mechanisms in the body which maintain a balance between coagulants and anticoagulants.

There are three steps in hemostasis—constriction of the damaged blood vessel which slows down the bleeding. The subendothelial tissues of blood vessels get exposed on injury and on coming in contact with platelets form a temporary hemostatic plug that arrests bleeding. A definitive clot is formed by meshwork of fibrin. A cascade of enzymatic reactions and clotting factors lead to conversion of the soluble plasma protein fibrinogen to insoluble fibrin. The fibrin threads bind to platelets bringing them tightly together. The clot formed retracts and dissolutes due to contraction of platelets and bridging the edges of wound together. The dissolution of clot is done by plasmin which restores normal blood flow to the healed tissue.

Coagulation Pathways

There are two pathways—extrinsic and intrinsic. The intrinsic pathway begins with activation of factor XII to XIIa on coming in contact with negatively charged surface. Kallekrein activates factor XIIa to XIIa. XIIa activates factor XI to XIa which in turn activates factor IXa which forms a complex with VIIIa. This complex activates factor X in presence of Ca^{2+} and platelet phospholipids. The extrinsic system is initiated by release of tissue thromboplastin released from vessel walls and other tissues when damaged. Tissue factor activates factor VII to VIIa, triggered by release of tissue thromboplastin that activates factor VII. Factor VIIa activates factor IX and X. In the presence of phospholipids, Ca and factor V, activated factor X catalyzes the conversion of prothrombin to thrombin. The action of thrombin on fibrinogen results in formation of monomers which polymerise to form long fibrin threads in presence of calcium and factor XIIIa (Fig. 23.1).

Prevention of Blood Clotting in Normal Vascular System

The most important factors for preventing clotting in the normal vascular system are (1) smoothness of the endothelium is a barrier to activation of the intrinsic clotting system. (2) a layer of glycocalyx, a mucopolysaccharide adsorbed to the inner surface of the endothelium, which pushes back the clotting factors and platelets. (3) A protein bound with the endothelial membrane, thrombomodulin which binds thrombin and activates protein

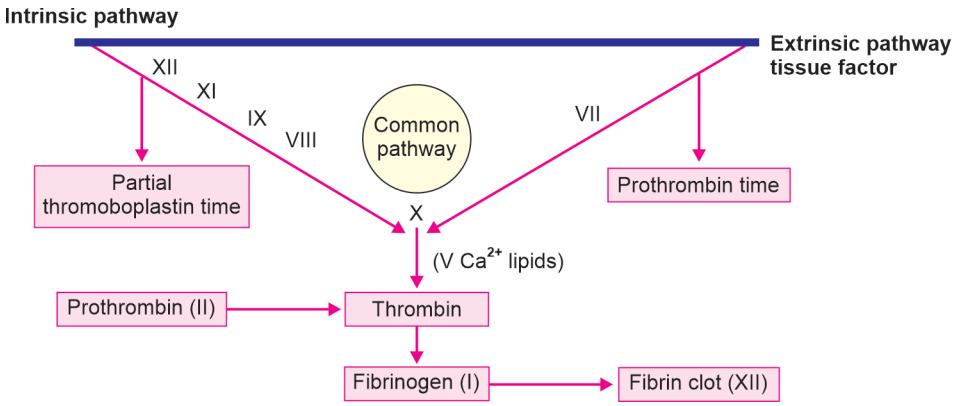

Fig. 23.1: Coagulation cascade

C that acts as anticoagulant by inactivating factors V and VIII. The two most powerful of anticoagulants are fibrin threads formed during the process of clotting and alpha globulin called antithrombin III (Fig. 23.2).

Heparin sulfate is an anticoagulant present on the luminal surface of vascular endothelium. It prevents the activation of prothrombin to thrombin, inhibits the action of thrombin on fibrinogen, potentiates the action of antithrombin III which inactivates a number of coagulation factors including thrombin. Alpha-2 macroglobulin is a very large globulin molecule having a molecular weight 360,000. It functions as a binding agent for several coagulation factors and prevents their proteolytic actions.

Anticlotting mechanisms: The clot formation is balanced by interaction between platelet aggregating effect of thromboxane A2 and the antiaggregatory effect of prostacyclins. Antithrombin III is a circulating protease inhibitor. It binds to serine proteases with help of heparin, in the coagulation system, blocking their activity as clotting factors. The endothelium of the blood vessels is protective in preventing the extension of clots. All endothelial cells except those in the cerebral circulation produce thrombomodulin which forms thrombomodulin thrombin complex which activates protein C along with cofactor protein S, which are anticoagulants.

Plasmin: The plasma proteins contain plasminogen which on activation becomes plasmin. Plasmin lyses fibrin and fibrinogen. The injured tissues and vascular endothelium release a powerful activator called tissue plasminogen activator a day after the clot has stopped bleeding. It converts plasminogen to plasmin and removes the clot.

Pathology and treatment of bleeding disorders: Bleeding is caused by vitamin K deficiency, haemophilia, thrombocytopenia, excessive oral anticoagulant therapy.

1. Except III, IV, VIII factors, almost all the blood clotting factors are formed by the liver. Diseases of the liver such as hepatitis, cirrhosis, acute yellow atrophy can depress the clotting system causing a severe tendency to bleed. Vitamin K deficiency is another cause of depressed formation of clotting factors by the liver. Vitamin K is required for formation of factor II, factor VII, IX and X. The intestinal tract bacteria continually synthesize vitamin K. If the liver fails to secrete bile into intestine, it causes poor fat absorption and also poor vitamin K absorption. If vitamin K is given to a deficient person 4–8 hours prior to surgery and the liver parenchymal cells are ½ normal, sufficient clotting factors will be produced to prevent excessive bleeding during the procedure.

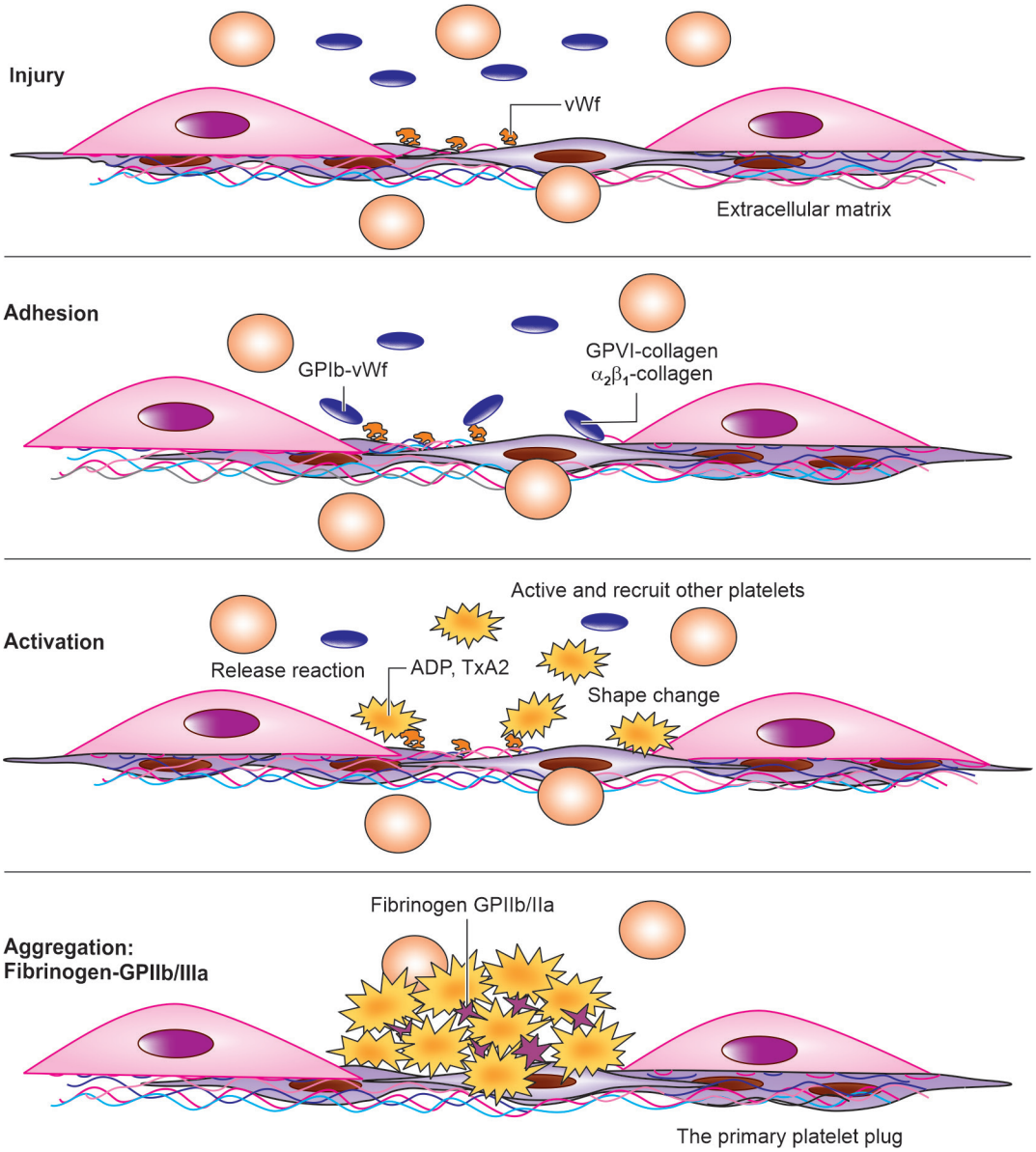

Fig. 23.2: Blood clotting mechanism

2. Hemophilia is caused by factor VIII deficiency and von Willebrand (VW) factor deficiency. It is cause of bleeding disorder due to reduced platelet adhesion and by lowering plasma VIII. Hemophilia has been treated with factor VIII rich preparations made from plasma produced by recombinant DNA techniques. Some patients with von Willebrand disease are treated with desmopressin which stimulates production of factor VIII, prior to dental procedures or surgery. Pure recombinant proteins of factors VIII and IX are now available.

3. Thrombocytopenia: It means the lowering of platelet counts in the circulatory system. The patients have tendency to bleed when the platelets fall below 50,000/microliters, due to bleeding from many small venules or capillaries. The skin of such a person displays many small purplish blotches, giving the name thrombocytopenic purpura. Idiopathic thrombocytopenia is a result of developing autoimmunity to the person's own platelets. Relief from bleeding for 1–4 days can be affected in idiopathic thrombocytopenia purpura (ITP) by giving fresh whole blood transfusions. Splenectomy is helpful and complete cure because the spleen stores and filters blood and makes white blood cells that protect from infection.

Coagulants are agents which promote coagulation of blood and are useful in hemorrhagic states. Fresh whole blood/plasma provide all the factors needed for coagulation and clotting factors.

Classification

- Vitamin K_1—is found in plant food and called phytonadione.
- Vitamin K_2—menoquinones are synthesized by intestinal bacteria.
- Vitamin K_3—fat-soluble—menadione sodium bisulfate.
- Miscellaneous—fibrinogen
- Antihemophiliac factor
- Desmopressin
- Adenochrome monosemicarbazone
- Rutin, ethamsylate

Vitamin K: It is fat-soluble vitamin, used for synthesis by liver of coagulation proteins—II, VII, IX and X.

Fat soluble forms of vitamin K are absorbed with help of bile salts from intestine through lymphatics. Deficiency of vitamin K occurs due to liver disease, obstructive jaundice, malabsorption, long-term antimicrobial therapy.

Use: Vitamin K is used in prophylaxis and treatment of bleeding due to deficiency of clotting factors, e.g. liver failure, bleeding disorders, esophageal varices, multiple organ dysfunction. Vitamin K IM is given for 3 days. In multiple organ dysfunction, given for one week. In obstructive jaundice or malabsorption syndromes, vitamin K, 10 mg IM/day or orally along with bile salts is given. In newborns, vitamin K is given 1 mg IM soon after birth because of low levels of clotting factors. In severe bleeding due to oral anticoagulants, 10 mg IM is given followed by 5 mg 4 hourly.

Fibrinogen: Controls bleeding in hemophilia, anti-hemophiliac globulin deficiency and acute afibrinogenic states.

Antihemophiliac factor—is concentrated human antihemophilic globulin (AHG) derived from pooled human plasma.

Desmopressin—releases factor VIII and von Willebrand's factor from vascular endothelium and checks bleeding in hemophilia and von Willebrand's disease.

Adenochrome monosemicarbazone—reduces capillary fragility, controls oozing from raw surfaces and prevents bleeding from microvessels, e.g. epistaxis, hematuria, secondary haemorrhage from wounds.

Ethamsylate: The dose is 250–500 mg TDS till bleeding stops. It works by increasing the ability of platelets to stick together and form blood clots. It reduces capillary bleeding when platelets are adequate. Used in treatment of capillary bleeding in menorrhagia, after abortion, postpartum hemorrhage (PPH), epistaxis, melena, hematuria and after tooth extraction.

Tranexamic acid: It helps by slowing the breakdown of blood clots which helps to prevent prolonged bleeding. 250–500 mg TDS in any bleeding. 100 ml (500 mg) in 100 ml NS over half an hour.

Epsilon aminocaproic acid (EACA)—is antifibrinolytic agent, used 5 g oral/IV followed by 1 g hourly till bleeding stops. It is useful in hematuria, obstetric complications, bleeding P/V. The side effect is muscle necrosis.

In case of blood transfusion, it should be done over 4–5 hours.

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Chapter
24

Treatment of Thromboembolic Disorders

PATHOPHYSIOLOGY OF CLOTS AND THROMBI

Thrombus is an intravascular clot. Three factors—Virchows triad, predispose to thrombosis: (1) The vascular endothelial injury occurs in chronic and sustained hypertension, ulcerated atherosclerosis, arterial diseases, etc. This is the site of clot formation. (2) Sluggishness of bloodflow promotes thrombosis. (3) Hypercoagulability of blood—increased activity of procoagulants such as fibrinogen, prothrombin and other coagulants lead to thrombosis. The major complication of thrombosis is thromboembolism. Emboli dislodge from the thrombus and through microcirculation travel to visceral organs such as brain (cerebral embolism), lungs (pulmonary embolism), heart (coronary embolism) and intestine (intestinal embolism). Coronary and cerebral thrombosis lead to infracts causing ischemic tissue death, presenting as heart attack and stroke, respectively.

1. Disseminated intravascular coagulation (DIC) is widespread intravascular coagulation that occurs due to procoagulants due to tissue factor exposure to blood. This is usually seen in septic abortions, amniotic fluid embolism, gram negative septicemia, fungemia, severe trauma, burn sepsis, snake bite, some hemolytic trabsfusion reactions. It clinically manifests as multiorgan dysfunctions caused by widespread microembolisms, and bleeding caused by consumption of platelets, fibrinogen, factors V and VIII. Congenital absence of protein C leads to uncontrolled DIC. Resistance to protein C is another cause. The lab findings are thrombocytopenia, hypofibrinogenemia, increased d-dimer and fibrin degradation product, and prolonged partial thromboplastin time, prothrombin time, and thrombin time.
2. Diabetes with their predisposition to severe atherosclerosis are vulnerable to arterial thrombi. Thrombi may develop in cardiac chambers when there is injury to the endocardium as in cardiac surgery, infections of the myocardium. Inflammatory valve diseases or prosthetic valves are favored sites of thrombus formation. The hemodynamic stress in hypertension or turbulent flow in arterial disorders is injurious to endothelial cells. Radiation injury, cigarette smoke, hypercholesterolemia, homocysteine and immunological injuries in transplant rejection, immune complex deposition cause potent thrombogenic influence.
3. Alterations in normal blood flow with turbulence contribute to the development of arterial and cardiac thrombi while stasis contribute to venous thrombosis. Thrombi often form overlying ulcerated atheromatous plaques. Thrombi are prone to occur in the aorta and

arteries within abnormal dilatations referred to as aneurysms. In healed rheumatic heart disease (RHD), mitral stenosis causes left atrium to expand and fail to empty. When Atrial fibrillation supervenes, atrial and auricular thrombosis occurs.

Stasis in the slowly moving venous circulation causes thrombi, e.g. in abnormally dilated varicose veins, as thrombi arise in pockets created by venous valves due to stasis or turbulence. Hyperviscosity syndromes—(polycythemia, cryoglobulinemia and macroglobulinemia) increase resistance to flow and induce stasis in small vessels.

4. Deficiency of antithrombin III or protein C, nephrotic syndrome following severe trauma, disseminated cancer and during late pregnancy and following delivery are prone. Race, age, smoking, obesity, bed rest, immobilization create a high risk. Advancing age due to hypercoagulability, reduced physical activity with poor venous drainage from the legs, underlying atherosclerosis with endothelial injury, with some cardiac failure with sluggish circulation, decompensated cardiac failure is a risk. Tissue damage related to soft tissue trauma, fractures, burns, postoperative state predispose.
5. Myocardial infarction and cerebral infarction are related to thrombi in atherosclerotic vessels. Arterial thrombi in small vessels cause infarction of the dependent tissues. Most arterial emboli originate within the heart. They always cause infarction. Whereas venous thrombi cause collateral bypass channels to enlarge to maintain venous drainage of the affected part. Venous thrombi of legs may embolize to lungs. Half of thrombi in large veins of legs—popliteal, femoral, and iliac, are asymptomatic and embolize to cause death.

Thromboembolic Conditions

An abnormal clot that develops in a blood vessel is called a thrombus. Once a clot has developed, continued flow of blood past the clot is likely to break it away from its attachment and such freely flowing clots are known as emboli. First, any roughened endothelial surface of vessel–caused by arteriosclerosis, infection or trauma is likely to initiate the clotting process. These are removed from the blood by the macrophage system, mainly by Kupffer cells of the liver. Genetically engineered tissue plasminogen activator (PA) is now available in treating intravascular clots.

Anticoagulants

The anticoagulants inhibit the action of the coagulation factors or interfere with the synthesis of coagulation factors.

Heparin

Heparin occurs naturally as a macromolecule complexed with histamine in mast cells. It is extracted for commercial use from porcine intestinal mucosa.

It is injectible, rapidly-acting anticoagulant that interferes with formation of thrombi.

Structure and mechanism of action: Unfractionated heparin is a mixture of straight chain, an-ionic glysoaminoglycans with wide range of molecular weights. It is strongly acidic because of presence of sulfate and carboxylic acid groups. When heparin molecules bind to antithrombin III, conformational change occurs that catalyses the inhibition of thrombin 1000-fold.

Low molecular weight heparin (LMWHs) are produced by enzymatic depolymerization of unfractionated heparin, e.g. enoxaparin, dalteparin, tinzaparin. It complexes with antithrombin III and inactivate factor Xa.

Heparin in higher doses inhibits platelet aggregation and prolongs bleeding time.

It causes lipemia clearing by releasing lipoptrotein lipase from the vessel wall and tissues. Low concentration of heparin prolongs activated partial thromboplastin time (APTT) without prolonging prothrombin time (PT). High concentration prolongs both.

Unfractionated heparin and the LMWHs limit the expansion of thrombi by preventing fibrin formation.

Uses: These agents are used for treatment of venous thromboembolism—deep vein thrombosis (DVT) or pulmonary embolism (PE).

- These are also used for prophylaxis of postoperative venous thrombosis in patients undergoing surgery or those with acute MI.
- These drugs are anticoagulants of choice for treating pregnant women, because they do not cross placenta due to their large size and negative charge.
- Unfractionated heparin can be given in renal dysfunction.

Route of administration and dosage: Heparin must be administered subcutaneously or IV as it is unable to cross cell membranes. Heparin is administered as IV bolus 5000–10000 U to achieve immediate anticoagulation. This is followed by low doses or continuous infusion of heparin 750–1000 U/hr, titrating the dose so that activated APTT is 1.5–2.5-fold the patients. 5000 U SC is injected every 12 hours before surgery and continued for 7–10 days or till the patient starts moving about to prevent postoperative deep vein thrombosis.

Pharmacokinetics: In the blood, heparin binds to many proteins that neutralise its activity causing unpredictable pharmacokinetics. The anticoagulant effect with heparin occurs within minutes of IV administration or 1–2 hours after subcutaneous injection. Best response is with IV infusion as other routes give large variation in response.

Heparin is taken up by monocyte/macrophage system, and it undergoes depolymerisation and desulfation to inactive products. The inactive metabolites and some of the parent heparin is excreted in urine. The half-life of heparin is 1.5 hours whereas half-life of LMWHs is longer than that of heparin—3–12 hours.

Advantages of LMWHs: Better subcutaneous bioavailability—70–90% compared to unfractionated heparin (UFH) (20–30%), variability in response is minimised.

Long-lasting effect and dose independent clearance pharmacokinetics.

Since APTT time is not prolonged, lab monitoring is not needed, dose is calculated on body weight basis.

Adverse effects: The chief complication of heparin and LMWH therapy is bleeding. Excess bleeding may be managed by discontinuing the drug or by treating with protamine sulfate. When infused slowly, the latter combines ionically with heparin to form a stable 1:1 inactive complex.

Heparin-induced thrombocytopenia (HIT) is a serious condition. Osteoporosis has been observed in patients on long-term heparin therapy.

Unfractionated heparin and LMWH are contraindicated in patients who have hypersensitivity to heparin, in bleeding disorders, alcoholism or who have recent surgery of the brain, eye, or spinal cord.

Danaparoid—is composed of heparin sulfate, dermatan sulfate and chondroitin sulfate, is greater factor X specific than LMWH. Bleeding due to it is not reversed by protamine.

Oral Anticoagulants

Warfarin prevents the reduction of inactive vitamin K to active vitamin K and inhibit the synthesis of vitamin-dependent clotting factors–II, VII, IX and X by blocking γ carboxylation

of glutamate residue in these factors. Some patients do not respond to warfarin, i.e. genetic resistance which is due to mutational changes in the enzyme vitamin K epoxide reductase.

Onset of action of warfarin occurs in 8–10 hours but full effect comes over a period of 1–3 days when all clotting factors disappear. Adequate dose of vitamin K can overcome the effect of even large dose of oral anticoagulant. The anticoagulant effect may be preceded by a transient period of hypercoagulability. This is caused by rapid decrease in protein C levels.

Commercial or racemic warfarin is a mixture of R and S enantiomers. The S form is more potent and metabolised by ring oxidation. It is glucuronidated and excreted in urine. It crosses placenta and secreted in milk. Loading dose is 5–10 mg.

Acenocoumarol: The half-life is 8 hours but an active metabolite is produced so that overall effect is 24 hours. Loading dose is 8–12 mg.

They are well-absorbed orally and extensively bound to plasma proteins. The oral absorption of warfarin is rapid and complete. It undergoes extensive hepatic metabolism. Both forms undergo glucuronide conjugation to be excreted in urine. Oral anticoagulants cross placental barrier and cause fetal malformations, thus avoided during pregnancy.

Uses: Warfarin is used for the maintenance therapy after initial treatment with heparin for pulmonary embolism and DVT. It cannot be used for initiation of therapy because of delayed onset of action. Should be taken at bedtime as single daily dose. Warfarin is used for prophylaxis of PE, DVT, thromboembolism episodes in patients undergoing surgery, hip or knee, prosthetic valve, and chronic atrial fibrillation. Warfarin may be used before the conversion of AF to sinus rhythm. Cerebral stroke is common in patients with atrial fibrillation and warfarin is used—5–15 mg oral daily. Warfarin therapy requires international normalised ratio (INR) monitoring to keep INR between 2–3 for most indications.

Adverse effects: Bleeding is the commonest adverse effect. The most common site of bleeding is observable (e.g. skin, mucus membrane) or occult (renal tract, GIT and brain, hepatic, pulmonary, uterine). Oral phytonadione–vitamin K_1 is used however fresh frozen plasma to provide clotting factors and vitamin K_1 10 mg required as IV infusion in emergency.

Skin necrosis, teratogenic effect and abortion may occur.

The factors that reduce its therapeutic effect are hypothyroidism, in pregnancy, consumption of large amount of food or supplements rich in vitamin K and drugs, e.g. cholestyramine, sucralfate, enzyme inducers, e.g. barbiturates, primidone, carbamazepine, rifampicin and griesofulvin.

Rivaroxaban—is direct activated factor Xa inhibitor. It is rapid acting with duration of action 24 hrs. It is indicated for prevention of venous thromboembolism after elective hip or knee replacement surgery. It is also effective for prevention of DVT and prevention of thrombosis in cases of atrial fibrillation. It has good therapeutic index and devoid of significant interactions unlike warfarin. 15 mg/day BD for 3 weeks followed by 20 mg/day for treatment of DVT and PE.

Fondaparinux: Is a penta-saccharide anticoagulant that is synthetically derived. This agent inhibits only factor Xa. Useful in Deep vein thrombosis and pulmonary embolism and for prophylaxis of venous thromboembolism in setting of orthopedic and abdominal surgery. It is eliminated in urine mainly as unchanged drug with an elimination half-life of 17–21 hrs. It is contraindicated in patients with severe renal impairment. It can be used in patients with allergy to heparin. 2.5 mg SC OD.

Dabigatran etexilate: Is oral direct thrombin inhibitor with efficacy equal to LMWH and warfarin. It is well absorbed orally and rapidly blocks catalytic site of thrombin. Bleeding is

common side effect. It is used for prevention of venous thromboembolism after elective hip or knee replacement surgery. The dose is 150 mg oral BD. It is contraindicated in patients with mechanical prosthetic heart valves. It should be used with caution in renal impairment and elderly.

Parenteral direct thrombin inhibitors: Argatroban is a synthetic parenteral analogue of arginine. It is direct thrombin inhibitor used for prophylaxis or treatment of venous thromboembolism in patients with HIT and is approved for use during percutaneous cardiac intervention (PCI) with risk of HIT. Because argatroban is metabolised in the liver, it may be used with caution in patients with hepatic impairment. IV bolus 350 mg/kg followed by 25 μg/kg/min infusion.

Bivalirudin and desirudin: These are parenteral anticoagulants that are analogs of hirudin, a thrombin inhibitor derived from leech saliva. Bivalirudin is an alternative to heparin in patients undergoing PCI who have risk of developing HIT and also in patients with unstable angina undergoing angioplasty. Dosage adjustment is required in patients with renal impairment. Bivalirudin—0.75 mg/kg bolus IV inj. followed by 1.75 mg/kg/hr IV infusion.

Desirudin is indicated for prevention of DVT in patients undergoing hip replacement surgery.

Uses of Anticoagulants

The aim of using anticoagulants is to prevent thrombus extension and embolic complications by reducing rate of fibrin formation. Heparin is used for rapid and short lived action while oral anticoagulants are suitable for maintenance therapy.

1. **Deep vein thrombosis and pulmonary embolism:** When DVT/pulmonary embolism has occurred, immediate LMW heparin followed by warfarin therapy should be instituted. The dose is 1000 IU @5 ml/hr. LMW heparin/fondaparinux have now replaced UFH except in case of major surgery and in high risk cases because action of UFH can be terminated rapidly.
2. **MI:** Heparin IV 5000 U@5 ml/hr or preferably LMW heparin/fondaparinux SC once or twice daily for 2–8 days followed by oral anticoagulants for 3 months are generally given after recanalization of coronary artery by fibrinolytic therapy.
3. **Unstable angina:** Short-term use of heparin has reduced the occurrence of MI in unstable angina patients.
4. **Rheumatic heart disease, atrial fibrillation:** Low-dose heparin.
5. **CVS disease:** Used in cerebral embolism.
6. **Vascular surgery, prosthetic heart valves, retinal vessel thrombosis, extracorporeal circulation, hemodialysis:** Anticoagulants are indicated along with antiplatelet drugs for prevention of thromboembolism.
7. **Defibrination syndrome or DIC:** Occurs in abruptio placentae, certain malignancies and infections. Enoxaparin, dalteparin, rabeparin are used in pulmonary embolism, myocardial infarction (MI), DVT, left atrial clot, CVA-ischemic but not recommended in old age due to osteoporosis as side effect.

Antiplatelets

Platelet aggregation inhibitors decrease the formation of platelet rich clot or decrease the action of chemical signals that promote platelet aggregation.

- The platelet aggregation inhibitors described below inhibit phosphodiesterase III (PDE III), cyclo-oxygenase 1 (COX 1) or block glycoprotein (GP) IIB/IIIa or ADP receptors, interfering with signals that promote platelet aggregation.
- Because these agents have different mechanism of action, synergistic or additive effects may be achieved when agents from different classes are combined.
- These agents are used in prevention and treatment of occlusive CVS diseases, in the maintenance of vascular grafts and arterial patency and as adjuncts to thrombin inhibitors or thrombolytic therapy in MI.
- **Process of platelet aggregation:** Stimulation of platelets by thrombin, collagen, ADP results in activation of membrane phospholipids that liberate arachidonic acid from membrane phospholipids. Arachidonic acid is converted to prostaglandin H2 (PGH2) by COX1. PGH2 is further metabolised to thromboxane A2 (TXA2), which is released into plasma. TXA2 promotes the aggregation process that is essential for the rapid formation of a hemostatic plug.

Antiplatelet Drugs

Aspirin inhibits TXA2 synthesis in platelets by irreversible acetylation of active serine site of COX1, thereby irreversibly inactivating the enzyme that catalyses an early step in TxA2 synthesis. For this reason, aspirin inhibits platelet aggregation for their total life span 7–10 days.

- Aspirin also inhibits PGI2 synthesis in vessel wall. At low doses, TXA2 days formation is suppressed whereas high doses >900 mg/day may decrease both TXA2 and prostaglandin I2 (PGI2) production. It also inhibits release of ADP from platelets and their sticking to each other.
- Because aspirin exhibits a longer antiplatelet effect, it is administered once a day dose (75–150 mg) or every other day dose (350 mg) alone or coadministered with clopidogrel/prasugrel.

Therapeutic uses: Aspirin is used in prophylaxis of transient cerebral ischemia, to reduce the incidence of recurrent MI and to decrease mortality in primary and secondary prevention of MI. Complete inactivation of platelets occurs with 75 mg of aspirin given daily. The recommended dose of aspirin ranges from 50–325 mg/day.

- **P. Kinetics:** Bleeding time is prolonged by aspirin treatment causing complications that include increased incidence of hemorrhagic stroke and GI bleeding specially at higher doses of the drug.
- NSAIDs such as ibuprofen inhibit COX1 by transient competing at the catalytic serine site. Ibuprofen if taken within 2 hrs prior to aspirin, can obstruct the access of aspirin to the serine residue and thereby antagonise platelet inhibition by aspirin.

Dipyramidole—is a coronary vasodilator, increases intracellular levels of cAMP by inhibiting cyclic nucleotide PDase, resulting in decreased TXA2 synthesis. It may potentiate the effect of Prostacyclin to antagonise platelet stickiness and decrease platelet adhesion to thrombogenic surfaces. Dipyramidole is used for stroke prevention and given in combination with aspirin. Dipyramidole has variable BA following oral administration. The drug undergoes hepatic metabolism as well as glucuronide conjugation and excreted in faeces. Patients with unstable angina should not use dipyramidole, which may worsen is chemia. (coronary steal phenomenon). Dipyramidole commonly causes headache and can lead to orthostatic hypotension. Dose—150–300 mg/day.

Platelet ADP receptor inhibitors: Ticlopidine, clopidogrel, prasugrel and ticagrelor are P2Y12 ADP receptor inhibitors that also block platelet aggregation by a mechanism different from that of aspirin.

- These drug inhibits the binding of ADP to its receptors on platelets and inhibit the activation of the GPIIb/IIIa receptors required for platelets to bind to fibrinogen and to each other. Within seconds of vascular injury, the exposed collagen of the underlying connective tissue activates the dormantly lying glycoprotein integrin receptors on platelets which triggers release of ADP and 5HT along with calcium and other fibrin stabilising factors. ADP activates ADP receptors on platelets to induce shape change and aggregation (P2Y1 effect) and to increase their adhesiveness (P2Y12 effect) Chapter 23 (Fig. 23.2).
- **Ticagrelor:** Binds to P2Y12 ADP receptor in a reversible manner. It is indicated for prevention of transient ischemic attacks (TIA) and stroke in patients with prior cerebral thrombotic event. Ticagrelor is approved for the prevention of arterial thromboembolism in patients with unstable angina and acute MI, including those under percutaneous coronary intervention (PCI).
- However, due to life threatening hematological adverse reactions (neutropenia), ticlopidine is reserved for patients who are intolerant to other therapies. The dose is 250 mg BD with meals.
- Antiplatelet effect achieved in 1–3 hrs with ticagrelor, 2–4 hrs with prasugrel, 3–4 days with ticlopidine.
- **Clopidogrel**—is approved for prevention of atheroscleotic events in patients with recent MI or stroke and in those with established peripheral arterial disease. It is also approved for prophylaxis of thrombotic events in acute coronary syndromes. Clopidogrel is used to prevent thrombotic events associated with PCI with or without coronary stenting. Clopidogrel 75 mg OD is a prodrug and its therapeutic efficacy relies on its active metabolite, which is produced via metabolism by CYP2C19. Other drugs that inhibit CYP2C19, such as omeprazole and esomeprazole, should not be administered concurrently with clopidogrel.
- **Prasugrel**—is approved to decrease the thrombotic CVS events in patients of acute coronary syndromes. Loading dose 60 mg, followed by 10 mg OD.
- **Pkinetics:** These agents require loading dose for quicker antiplatelet effect. Food interferes with absorption of ticlopidine. After oral ingestion, the drugs are extensively bound to plasma proteins. They undergo hepatic metabolism by cyt P450 enzyme to active metabolites. Elimination of drugs and metabolites occur by renal and fecal routes.

Adverse effects: These agents can cause prolonged bleeding. Ticlopidine is associated with severe hematological reactions such as agranulocytosis, thrombotic thrombocytopenic purpura (TTP) and aplastic anemia.

Clopidogrel causes fewer adverse reactions and incidence of neutropenia is lower. Prasugrel is contraindicated in patients with history of transient ischemic attack (TIA) or stroke.

- **Glycoprotein (GP) IIb/IIIa receptor antagonists—abciximab, eptifabatide and tirofiban:** They interrupt the interaction of fibrinogen and von Willebrand factor with the platelet GPIIb/IIIa complex and inhibit aggregation of platelets activated by various stimuli.
- **Therapeutic uses:** These agents are given IV along with heparin and aspirin, as adjunct to PCI for prevention of cardiac ischemic complications.
- Abciximab is also approved for patients with unstable angina not responding to conventional medical therapy when PCI is planned within 24 hrs. Abciximab is given by IV bolus followed by IV infusion, achieving brisk antiplatelet inhibition in 30 min. After

cessation of abciximab infusion, platelet function gradually returns to normal, with the antiplatelet effect persisting for 24–48 hours. When IV infusion of eptifibatide or tirofiban is stopped, both agents are rapidly cleared from the plasma.

The major adverse effect of these agents is bleeding, especially if used with anticoagulants.

- Cliostazol is an oral antiplatelet agent that also has vasodilating activity. Cliostazol and its active metabolites inhibit PDase type III which prevent degradation of cyclic adenosine monophosphate (cAMP) level in platelets and vascular tissues. The increase in cAMP in platelets and the vasculature prevent platelet aggregation and promote vasodilation of blood vessels. It favourably alters the lipid profile, causing a decrease in plasma triglycerides (TGs) and an increase in high-density lipoprotein (HDL).

  The drug is approved to reduce the symptoms of intermittent claudication. Cliostazol is extensively metabolised in liver by CYP3A4 2C19 and 1A2 isoenzymes. The primary route of elimination is kidney. Headache and GIT side effects are common adverse effects. PD ase type III inhibitors increase mortality in patients with advanced heart failure. Cliostazol is contraindicated in patients with heart failure.
- Nafidofuryl oxalate is a metabolic enhancer. It enhances supply of ATP by activating enzyme succinate dehydrogenase, also reduces 5HT-induced vasoconstriction and platelet aggregation by blocking 5HT2 receptors. It is useful in obstructive disease with intermittent claudication by increasing the walking distance. The dose is 100 mg BD.

Uses of Antiplatelet Drugs

a. Low-dose aspirin (≤100 mg) started immediately after MI has been found to reduce mortality and prevent reinfarction. Ticlopidine and clopidogrel are alternatives. Aspirin is used to prevent re-occlusion after thrombolytic therapy. Ticlopidine, clopidogrel or apciximab used along with aspirin improve the outcome of percutaneous transluminal coronary angioplasty (PTCA) and stent procedures.
b. **Unstable angina:** Aspirin prevents coronary thrombosis in unstable angina as add on to thrombolytic therapy. Reduces recurrence of thrombotic stroke, reduces the risk of progression to MI and sudden death. For maximum benefit, aspirin is given along with heparin followed by warfarin.
c. **Cerebrovascular disease:** Antiplatelets do not alter the course of disease due to cerebral thrombosis. However, aspirin has reduced the incidence of transient ischemic attack (TIAs), of stroke in patients with transient ischemic attacks (TIAs) or persistent atrial fibrillation and those with history of stroke in the past.
d. **Prosthetic heart valves and AV shunts:** Antiplatelet drugs like dipyridamole used with warfarin reduce formation of microthrombi on artificial heart valves and the incidence of embolism.
e. Abciximab is used in conjunction with **angioplasty and stent procedures** and is additive with fibrinolytics.
f. Ticlopidine—orally is taken with food. Indicated for prevention of **thrombotic stroke** in patients who cannot tolerate aspirin.

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Chapter 25

Infections of Kidney and Urinary Tract

When there is intact local and systemic mechanisms in anatomically physiologically intact urinary tract, organisms are confined to the lower-end of the urethra.

Urinary tract infections (UTIs) are concerned with multiplication of organisms in the urinary tracts and defined by confirmation of more than 1 lac organisms per ml in collected midstream sample of urine.

The urinary tract infections can clinically present as asymptomatic bacteriuria, symptomatic acute urethritis and cystitis, acute prostatitis, acute pyelonephritis, septicaemia (usually by Gram-negative bacteria).

In domiciliary practice, *E. coli* accounts for 75% of all infections, remainder being due to *Proteus, Pseudomonas*, streptococci or *Staphylococcus epidermidis*.

The hospital acquired infections are due to organisms such as *Klebsiella* or streptococci but faecal *E. coli* still predominates. Hematogenous infections do occur but particularly in women. These are mostly due to ascending infections originating in the lower urinary tract.

A. UNCOMPLICATED AND COMPLICATED UTI

Uncomplicated UTI—occurs in anatomically and physiologically normal urinary tract with normal renal function and no associated disorder impairing defence mechanism (Fig. 25.1).

Complicated UTI—occurs in abnormal urinary tract with impaired renal function with disorder which impairs defence mechanisms, e.g. diabetes mellitus, immunosuppressive therapy, obstruction, calculi, vesicoureteric-reflux, neurological abnormality, chronic prostatitis, cystic kidney, analgesic nephropathy, and renal scarring.

Urinary tract infection pathology: The first stage is inhabitation of the periurethral zone with pathogenic faecal organisms. The urothelium of prone individuals may have more surface receptors to get attached to adherent strains of *E. coli*. The presence of short urethra in women and absence of bacterial male prostatic secretions is responsible for causing ascent of organisms into the bladder. Sexual intercourse can cause minor urethral trauma to the urethra and forces intercoital bacteria into the bladder. The bladder instrumentation readily introduces organisms.

Urine is a good culture medium and multiplication of organisms introduced into bladder depends on the size of the inoculum and virulence of the bacteria.

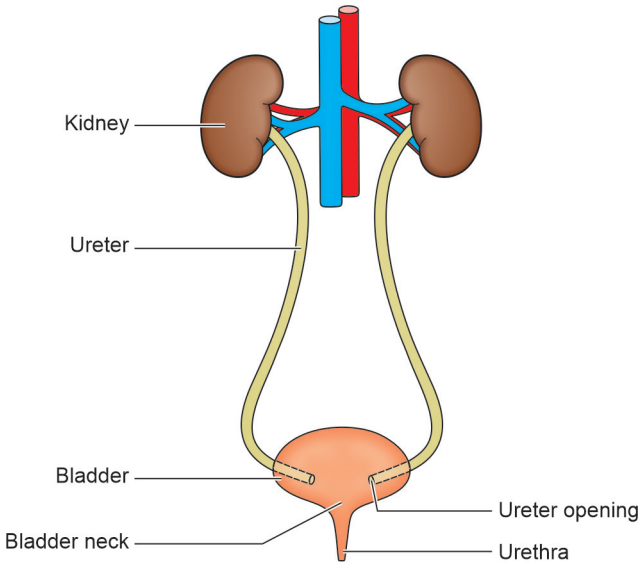

Fig. 25.1: Kidney ureter bladder system

The factors which hinder organisms multiplication in the urinary tract are:

- A high rate of urine flow
- When bladder is emptied regularly.
- Urinary glycosaminoglycans (Tamm Horsfall mucoprotein) which may bind to *E. coli*, thus preventing their attachment to urothelium,
- Intact defences of mucosa.

The urine which resides in bladder after voiding interferes with mucosal defence mechanisms. Thus, patients with obstruction below the bladder, gynaecological abnormalities, pelvic floor weakness or neurological problems are vulnerable to infection. Injury to the mucosa and presence of foreign body in the bladder also depress vesical defence mechanisms.

CLINICAL FEATURES

- An abrupt onset of frequency of micturition and dysuria.
- Burning pain is felt in the urethra during micturition while cystitis gives rise to suprapubic pain during and for a few moments after voiding.
- After the bladder voiding, there may be intense desire to pass more urine due to spasm of its inflamed wall.
- Suprapubic tenderness is often present and the urine may have unpleasant odour and appear cloudy.

The diagnosis depends on clinical features, demonstration of more than 1,00,000/ml organisms in a midstream urine sample (MSU) or any organism in urine from suprapubic aspirations. Pyuria is common, 2–3 pus cells/mm^3 are diagnostic.

PROPHYLAXIS IN RECURRENT UTI

- Plenty of fluid intake to at least 2 L/day
- Regular complete voiding of bladder

- Double micturition if reflux present.
- Urinating before and after intercourse.

Urinary Antiseptics

Some orally administered antimicrobials (AMAs) have antibacterial action, only in urine with no systemic antibacterial action, hence called urinary antiseptics.

Most UTIs are caused by Gram-negative bacteria, especially coliforms (*E. coli*). Chronic and recurrent infections may be mixed infections. Urine culture and sensitivity are very important to direct the choice of therapy.

Most AMA attain high concentration in urine. So, smaller than usual doses may be effective in lower UTI, because antibacterial action in urine is sufficient as the mucosa takes care of itself. In upper UTI, involving infections of kidney or ureters, doses are similar to those for any systemic infection because antimicrobial action in kidney tissue is needed.

Cotrimoxazole: May be employed empirically in acute UTIs without bacteriological data.

Given once daily bed time, cotrimoxazole 480 mg is used for prophylaxis of recurrent cystitis as well in catheterized patients.

It should not be used to treat UTI during pregnancy.

Quinolones: Norfloxacin, ciprofloxacin are highly effective against Gram-negative bacilli and at low cost.

Fluoroquinolones are valuable in complicated cases, those with prostatitis or indwelling catheters and for bacteria resistant to cotrimoxazole/ampicillin.

Norfloxacin given for 3 months may achieve cure in chronic UTI.

They should not be given during pregnancy.

Amoxycillin: Parenteral co-amoxiclav is often combined with gentamycin for initial treatment of acute pyelonephritis.

CHOICE OF DRUG

The least toxic and cheaper AMA should be used to eradicate the infecting organism

Choice of drug should be such that does not derange normal gut and perineal flora.

If urinary tract infection frequently recurs, chronic suppressive therapy with cotrimoxazole, nitrofurantoin, methenamine, cephalexin or norfloxacin may be given.

Antimicrobials Used for Acute UTIs

1. Norfloxacin 400 mg twice a day.
2. Ciprofloxacin 500 mg twice daily.
3. Ofloxacin 200–400 mg twice daily.
4. Cotrimoxazole 960 mg twice daily.
5. Cephalexin 250–500 mg 4 times a day.
6. Cefpodoxime proxetil 200 mg twice daily.
7. Amoxycillin + clavulanic acid (500 + 125) mg thrice daily.
8. Nitrofurantoin 100 mg twice a day for 5–7 days.

Treatment of Overactive Bladder/Urge Incontinence

- Oxybutynin 5 mg BD
- Tolterodine 1–2 mg BD
- Flavoxate 200 mg
- Dorifenacin 7.5–15 mg OD
- Solifenacin 5–10 mg OD, are vesicoselective anticholinergics used for treatment.

B. DISEASES OF KIDNEY

ACUTE PYELONEPHRITIS HAS FOLLOWING FEATURES

The renal pelvis is acutely inflamed and there is often coincident cystitis.

Sudden onset of pain in one or both loins, radiating in the iliac fossae and suprapubic area.

About 30% have dysuria and frequent passage of small amounts of cloudy urine due to associated cystitis.

Fever—38–40°C, rigors and vomiting, septicemia and hypotension supervene. Tenderness and guarding are present in the renal angle and lumbar region.

Markedly, there is leucocytosis.

The urine microscopy reveals numerous pus cells and organisms, some RBCs, epithelial cells.

REFLUX NEPHROPATHY

This is chronic interstitial nephritis resulting from UTI.

The most important feature is presence of coarse scars in the upper pole of kidney, each associated with contraction of the related papilla and dilation of the corresponding calyx.

The features can be identified by intravenous pyelogram (IVP)/micturating cystourethrogram (MCU). As the ureter passes through the vesical wall obliquely and is occluded during contraction of the bladder, it prevents reflex of urine from bladder into ureter during voiding.

Abnormalities of the intramural ureter allow reflux to occur and organisms from the bladder may then reach the kidney.

CHRONIC PYELONEPHRITIS

- Presence of hypertension or proteinuria on routine examination may be the first indication of the disease.
- Symptoms arising from urinary tract may also be present—frequency of micturition, dysuria, and aching lumbar pain.
- Occasionally, salt loss in urine results in weakness and fainting
- Pyuria and low-level proteinuria are common but not invariable.
- In pregnant women, permanent damage may occur from UTI. The hormonal changes of pregnancy cause ureteric motility and ureteric dilatation and may also facilitate infection in the renal parenchyma (Fig. 25.2).

C. ASSESSMENT OF KIDNEY FUNCTION

The assessment of kidney function is an essential step in recognition and monitoring of acute and chronic kidney diseases.

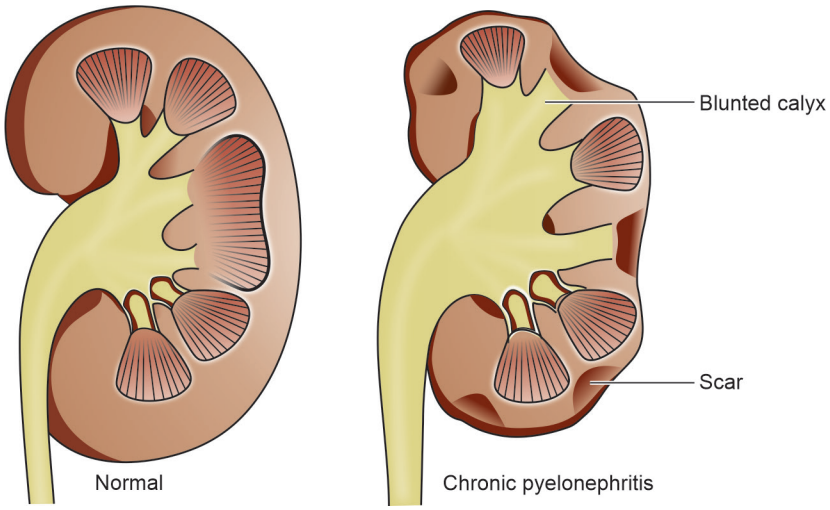

Fig. 25.2: Structure of normal kidney and chronic pyelonephritis

Pathophysiology—kidney function is best reflected by glomerular filtration rate (GFR). GFR is defined as sum of the filtration rate of all functional nephrons.

The normal GFR is 125 ml/min/1.73 m^2 in men and 100 ml/min/m^2 in women.

A decline in nephron numbers may not necessarily result in decline of GFR. Remaining nephrons can increase filtration rate to compensate, e.g. one might expect a 50% reduction in GFR after donation of a kidney. However, the measured GFR is often at 80% of pre-nephrectomy levels because of compensatory hyperfiltration in the remaining kidney.

An increase in GFR, as seen in early diabetic nephropathy, can reflect glomerular hyperfiltration, whereas, a fall in GFR can reflect kidney injury and disease.

Damage to the glomerular architecture may initially present with proteinuria only and damage to the tubules may result in solute wasting or concentration defects.

Structural diseases such as polycystic kidney disease, can be detected on USG prior to any change in GFR.

DIAGNOSTIC TESTING

Creatinine is a metabolic product, derived mainly from skeletal muscle cells and dietary meat. The typical daily production rate is 20–25 mg/kg/day.

A person with large muscle mass have higher creatinine production and level than those with a smaller mass.

The normal range for creatinine is reported between 0.8–1.4 mg/dl. The kidney eliminates creatinine by glomerular filtration and to a lesser extent by proximal tubular secretion.

In persons with normal kidney function, glomerular filtration accounts for >90% of creatinine elimination. Creatinine is not reabsorbed or metabolized to any significant degree in the kidney.

Creatinine is clinically used to track kidney function as it accumulates when renal elimination is compromised:

- An upward trend suggests a reduction in GFR.
- A downward trend in creatinine suggests an improvement in GFR.

- A small increase in creatinine at a lower concentration level signals a greater decline in renal function compared to small increase in creatinine when the baseline creatinine levels are high, e.g. a change of 1.0 to 1.4 mg/dl represents a greater decline in kidney function than a change of 3.0–3.4 mg/dl. Creatinine is not a perfect marker because of variable contribution of tubular secretion.
- As renal function declines, tubular secretion of creatinine increases, therefore, creatinine-based estimation of GFR overestimates renal function.

Urea: The elimination of urea by the kidneys is more complex than creatinine which renders blood urea nitrogen (BUN) a less useful marker of kidney function when evaluated in isolation. BUN can be increased by number of non-renal aetiologies, including-gastrointestinal bleeding, steroid use, parenteral nutrition. BUN can be reduced by malnutrition and liver diseases, which reduce urea generation rate.

For practical purpose, BUN is most informative when ratio of BUN/creatinine exceeds 20:1 which is suggestive of pre-renal state.

Clearance: Describes the quantity of fluid which is completely cleared of a marker over a definite period of time, expressed in ml/min.

The ideal marker should be biologically inert, completely filtered by the glomerulus, neither secreted nor absorbed and degraded by the kidney.

There are two widely used equations used to estimate kidney function in adults: Cockcroft-Gault equations and modification of diet in renal disease (MDRD) equation.

Cockcroft Gault equation—Estimated creatinine clearance

$$\text{Cr CL} = \frac{(140 - \text{Age}) \times \text{Weight (kg)} \times 0.85 \text{ (for females)}}{72 \times \text{Serum creatinine}}$$

The main pitfalls are:

Determining the patient's actual lean body weight and overestimation of true GFR by Cr CL with lower levels of kidney function.

Modification of Diet in Renal Disease (MDRD) Equation

Estimated GFR (ml/min/1.73 m^2) = 186 × S. creatinine × Age × 0.742 (if female) × 1.21 (if African American).

The MDRD and Cockcroft-Gault formula are less accurate:

- Overstimate GFR in critically ill Indian patients.
- The MDRD and Cockcroft-Gault equation may not be accurate in extremes of ages, i.e. They provide higher estimate at younger ages and lower estimates at older ages.
- Among patients of renal allograft recipient, these equations have variable accuracy.

The 24-hour CrCL is semigold standard to evaluate kidney function in clinical setting, when these equations may not be sufficiently accurate.

- CrCL can be measured by collecting a 24-hour urine sample and using the following formula: GFR = (U. creatinine × volume of urine/P. creatinine)/14440, where, U creatinine is the concentration of creatinine in urine. Volume of urine is the volume produced over 24 hours in ml.
- P. creatinine is the concentration of creatinine in plasma.

D. CLASSIFICATION OF GLOMERULOPATHIES

Nephrotic syndrome: Massive proteinuria >3.5 g/day, hypoalbuminaemia, oedema, lipiduria and hyperlipidaemia.

Acute glomerulonephritis: Haematuria, non-nephrotic range proteinuria, oedema, hypertension, transient renal impairment.

Rapidly progressive glomerulonephritis: Features of acute nephritis, focal necrosis and rapidly progressive renal failure over weeks.

Treatment: Dietary sodium restriction and a thiazide diuretic. Normal protein intake is advised.

Hypercoagulable state predisposes to venous thrombosis, so prolonged bed rest avoided and prophylactic anticoagulation required.

E. PATHOPHYSIOLOGY OF ACUTE KIDNEY INJURY (AKI) AND TREATMENT

AKI is defined as an abrupt deterioration in parenchymal renal function causing impairment of kidney filtration and excretory function reversible over a period of days or weeks.

If it is severe, it results in uremia and oliguria (Table 25.1).

Table 25.1: RIFLE classification of AKI

Grade	*GFR criteria*	*Urine output criteria (UO)*
Risk	↑Scr × 1.5 within 48 hr/↓GFR >25%	UO <1.5 ml/kg per hour × 6 hour
Injury	↑Scr × 2–3/↓GFR >50%	UO <0.5 ml/kg per hour × 12 hour
Failure	Scr × 3/↓GFR >75%	
Loss	Complete loss of kidney functions >4 weeks	UO <0.3 ml/kg per hour × 24 hour
ESKD	Persistent renal failure >3 months	

ESKD: End-stage kidney disease; Scr: Serum creatinine

Epidemiology: AKI is common, accounts for 5–7% of acute hospital admissions and up to 30% of admissions to the intensive care unit.

Risk factors for AKI include

1. Pre-existing chronic kidney disease (CKD)
2. Age/male sex
3. Comorbidity—diabetes mellitus (DM)/coronary artery discase (CAD), malignancy, chronic lung disease (CLD) and complex surgery.

Common Causes

- Volume depletion
- Sepsis
- Major surgical procedures

- Critical illness involving heart and liver failure
- Nephrotoxic medication administration
- Obstruction of the urinary tract.
- Envenomation from snakes, spiders, caterpillars, bees.
- Infectious causes such as malaria and leptospirosis
- Crush injuries and resultant rhabdomyolysis

Acute kidney injury is classified as: Pre-renal azotaemia, intrinsic renal parenchymal disease, post-renal obstruction.

Pre-renal azotemia is the most common form of AKI resulting from impaired perfusion of kidneys.

It is designated by a rise in S. creatinine or BUN concentration due to inadequate renal plasma flow and intraglomerular hydrostatic pressure to support normal GFR.

The most common clinical conditions associated with prerenal azotemia are: Hypotension, decreased cardiac output, use of NSAIDs and ACE inhibitors/angiotensin receptor blockers (ARBs).

It is rapidly reversible once parenchymal blood flow and intraglomerular hemodynamic is restored.

Prolonged periods of pre-renal azotaemia may lead to ischemic injury, termed as acute tubular necrosis.

Autoregulation: There are immediate neurohormonal systems directed at maintaining blood flow and GFR.

A decrease in BP leads to increased sympathetic activity, resulting in increased peripheral vascular resistance increasing cardiac output, leading to restoration of perfusion pressure. Sympathetic activity also stimulates release of renin through beta-adrenergic receptors.

Renal autoregulation maintains a constant level of renal blood flow despite fluctuations in arterial blood pressure based on the myogenic response and tubulo-glomerular feedback.

1. **Myogenic response:** A function of smooth muscle contraction in response to external stretching force causes afferent arteriolar constriction or dilation on fall or rise in arterial pressure.
2. **Tubulo-glomerular feedback leads** to afferent arteriolar dilation when macula-densa senses low solute delivery.

The Renin-angiotensin-aldosterone System (RAAS) is Critical in Renal Self-defense

With decreased renal perfusion, renin is released from juxtaglomerular (JG) cells—formation of angiotensin II resulting in efferent arteriolar constriction, enhanced renal tubular sodium reabsorption in early proximal tubule, increased release of aldosterone by the adrenals.

With modest hypotension or CHF, angiotensin can preserve GFR by preferential vasoconstrictive action on the efferent arteriole, causes increased intraglomerular pressure thus maintaining filtration fraction.

It increases release of antidiuretic hormone (ADH) from the posterior pituitary.

ADH is mainly synthesized by volume depletion and hyperosmolality causes maximum water conservation and excretion of concentrated urine.

Renal: There is intrarenal synthesis of vasodilator prostaglandins, kallikreins and kinins and nitric oxide.

Because of these autoregulatory mechanisms, renal function is able to be maintained even under conditions of diminished effective volume.

However, as the effective volume continues to decrease, the renal compensatory mechanisms may be overwhelmed as the afferent arteriolar dilation is no longer adequate to maintain flow.

Impaired autoregulation: Atherosclerosis, underlying standing hypertension and older age can lead to hyalinosis and myointimal hyperplasia causing structural narrowing of intrarenal arterioles and impaired capacity for renal afferent vasodilation.

Drugs can affect the compensatory changes to maintain GFR, e.g. NSAIDs inhibit renal prostaglandin production, limiting renal afferent vasodilation and ACE inhibitors and ARBs limit renal efferent vasoconstriction.

Post-renal uraemia results from obstruction of the urinary tract at any point from the calyces to the external urethral orifice. Some causes of acute tubular necrosis are haemorrhage, burns, diarrhoea and vomiting, fluid loss from fistulas, pancreatitis, diuretics, myocardial infarction, congestive cardiac failure, endotoxic shock, snake bite, myoglobinaemia, haemoglobulnaemia, hepatorenal syndrome, radiological contrast agents, drugs, e.g. aminoglycosides, NSAIDs, ACE inhibitors, platinum derivatives, abruptio placentae, pre-eclampsia and eclampsia.

Biochemical features: Hyperkalaemia is common following trauma to muscle and in haemolytic states, metabolic acidosis is usual.

Hyponatremia may be present due to fluid overload. Pulmonary oedema is common.

The uraemia symptoms present as anorexia, nausea, vomiting, pruritis followed by intellectual clouding, drowsiness, fits, coma and haemorrhagic episodes. Epistaxis and gastrointestinal haemorrhage are common.

Hypocalcaemia due to reduced renal production of 1,25-dihydrocholecalciferol and hyperphosphatemia due to retention of phosphate occur.

Treatment: It involves correction of hyperkalaemia and acidosis by sodium bicarbonate. Pulmonary oedema is corrected with IV furosemide.

Fluid and electrolyte balance is corrected.

Sodium intake and potassium restricted diet is advised.

Dialysis and hemofiltration is advised in case of: Uraemia, complications such as pericarditis, severe biochemical derangement, refractory hyperkalaemia, pulmonary oedema, severe acidosis, for removal of nephrotoxic drugs, e.g. gentamycin, lithium, aspirin.

Haemodialysis: Blood from the patient is pumped through an array of semipermeable membranes, which bring the blood into close contact with dialysate, flowing counter current to the blood.

There are certain disadvantages like haemodynamic instability, especially in acutely ill patients with multiorgan disease.

Rapid correction of uraemia in hemodialysis can lead to dialysis disequilibrium characterized by nausea and vomiting, restlessness, headache, hypertension, myoclonic jerking, seizures and coma.

F. PATHOPHYSIOLOGY OF CHRONIC KIDNEY DISEASE (CKD) AND ITS TREATMENT

It is longstanding (more than 3 months) and usually progressive (weeks to years) impairment in renal function.

Definition of CKD: (GFR <60 ml/ min/1.73 m^2).

It is characterized by abnormal kidney structure or function, present for >3 months with deleterious implications on health. The symptoms are common when the serum urea concentration exceeds 40 mmol/L.

The symptoms include: Malaise, loss of energy, loss of appetite, insomnia, nocturia, polyuria, itching, nausea, vomiting, diarrhoea, paresthesias, restless legs syndrome, bone pain due to metabolic bone disease, pulmonary oedema, symptoms due to anaemia, amenorrhoea in women and erectile dysfunction in men.

The most common causes of CKD are: Diabetes, glomerulonephritis, hypertension/ renovascular disease.

Pathophysiology

Mechanisms of damage involve:

1. Abnormalities in kidney development, toxin exposure
2. Hyperfiltration and hypertrophy of the remaining viable nephrons. The response to reduction in nephron number is mediated by—vasoactive hormones, cytokines, growth factors.

Eventually, these mechanisms become maladaptive as: The increased pressure and flow within the nephrons predisposes to:

1. Distortion of glomerular architecture
2. Abnormal podocyte function
3. Disruption of the filtration barrier

Leading to sclerosis and dropout of the remaining nephrons.

Increased intrarenal activity of RAAS also contributes to initial compensatory hypertrophy and sclerosis.

Virtually all organ systems are affected, but the most evident complications include: anaemia and associated easy fatiguability.

Abnormalities in calcium, phosphorus, and mineral regulating hormones such as 1,25-(OH)2D3 (calcitriol), parathyroid hormone and fibroblast growth factor, abnormalities of sodium, potassium, water and acid–base haemostasis occur.

In severe CKD, the toxins accumulate such that patients experience marked disturbance in:

- Activities of daily living and well-being.
- Nutritional status
- Water and electrolyte haemostasis.
- Immune complex deposition and inflammation.

In CKD, a host of metabolic and endocrine functions performed by kidneys are impaired and result in anemia, malnutrition, abnormal metabolism of carbohydrates, fats and proteins.

Investigations: Haematuria indicates glomerular nephritis.

Proteinuria is suggestive of glomerular disease. Do urine culture, urine sample for TB.

Serum: Urea and creatinine, calculation of eGFR

The complications of chronic kidney disease are anaemia, renal osteodystrophy-causing osteopenia leading to pseudofractures, subperiosteal erosions, pepper pot skull, rugger jersey spine.

Pruritis is common in severe CKD due to retention of nitrogenous waste products of protein catabolism, hypercalcemia, hyperparathyroidism, and hyperphosphatemia.

GIT complications include decreased gastric emptying, increased risk of reflux oesophagitis, peptic ulceration, acute pancreatitis and constipation.

Urate retention is common feature.

Insulin resistance and hyperprolactinemia and other endocrinal abnormalities may occur.

Severe uraemia causes an unusual combination of deranged cerebral function and decreased seizure threshold.

Median nerve compression in the carpel tunnel is common. Restless leg syndrome is common in uraemia.

Hypertension is a frequent complication of CKD. Hypertension and proteinuria are bad prognostic indicators.

Goals of treatment: Renoprotection—BP <130/80, proteinuria <0.3 g/24 hrs

Treatment

ACE inhibitors and ARBs are useful in patients with hypertension and proteinuria.

A new medication, aliskerin, functions through direct inhibition of renin and may have more potent effects if combined with ACE inhibitors.

Check potassium and renal function prior to and 1–2 weeks after starting treatment. Stop if potassium is >6 mmol/L, eGFR >25% of baseline.

Add calcium channel blocker if goals not achieved.

Add diuretic to prevent oedema, fluid overload, hyperkalemia and dietary restriction of potassium, ion exchange resins.

The anaemia of erythropoetin deficiency can be treated with epoetin-alfa 50–100 units/kg or long-acting darbepoetin subcutaneous every 2 weeks. A Hb level >13 g/dl during erythropoietin therapy have been associated with increased rates of blood clots, heart attacks, strokes, death. The complete blood count should be monitored at least monthly.

Hyperkalaemia is a potentially life-threatening complication of CKD. Restrict high potassium in the diet.

Sodium restriction is an essential component of management of oedema.

Consider sodium bicarbonate supplements for patients with eGFR <30. Maintaining bicarbonate levels above 22 mmol/L will help preserve bone histology and lessen the impact of acidosis in protein catabolism.

CKD causes increase in serum phosphate and reduced hydroxylation of vitamin D by kidney.

It is generally recommended to restrict phosphorus intake to 800–1200 mg/day and phosphate binders like calcium carbonate and acetate are used.

Also limit the amount of elemental calcium no more than 2000 mg/day.

In male erectile dysfunction, testosterone deficiency should be corrected. The oral phosphodiesterase inhibitors, e.g. sildenafil, tadalafil, vardenafil are effective.

Additional Measures

Statins to lower cholesterol to <4.5 mmol/L

Stop smoking, treat diabetes, normal protein diet—1g/kg bodyweight.

The Centre for Disease Control and Preventions Jan 2010 adult vaccination schedule recommends the most commonly administered vaccines to CKD are: Hepatitis B vaccine, pneumococcal vaccine and influenza vaccine

It is advisable to initiate dialysis in patients with CKD, secondary to diabetic nephropathy once the GFR is <15 ml/min.

In patients with CKD from other causes, dialysis may be delayed until GFR falls below 10 ml/min.

Long-term dialysis is started when it becomes necessary to manage one or more symptoms of renal failure:

- Inability to control volume status, including pulmonary oedema
- Inability to control BP
- Serositis
- Acid–base or electrolyte abnormalities
- Pruritis
- Nausea/vomiting/deterioration in nutritional status
- Cognitive impairment

Haemodialysis

Blood is passed over a semi-permeable membrane against dialysis fluid flowing in the opposite direction. It mainly involves diffusion of solute against concentration gradient.

Peritoneal dialysis uses the peritoneum as semi-permeable membrane. A catheter is inserted into the peritoneal cavity and fluid infused.

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Chapter 26

Treatment of Rheumatoid Arthritis and Gout

Etiopathogenesis and clinical signs and symptoms: Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease involving small and large joints of the extremities symmetrically. The onset of joint pain and swelling are usually insidious progressing slowly and fluctuating. In early disease, most commonly involved joints are metacarpophalangeal joints, interphalangeal joints, metatarsophalangeal joints. The wrists, elbows, shoulders, knees and ankles are also affected. It is an autoimmune disease involving joint inflammation, synovial proliferation and destruction of articular cartilage (Fig. 26.1). Immune complexes composed of immunoglobulin M (IgM) activate complement and release cytokines–mainly tumor necrosis factor-α (TNF-α) and interleukin-1 (IL1) which are chemotactic for neutrophils. These inflammatory cells secrete lyzosomal enzymes which damage cartilage and erode bone, while prostaglandins (PGs) produced in the process cause vasodilation and pain.

Fatigue is a common complaint. The symptoms are worse in the morning. Sleep is disturbed. The joints are usually warm and tender with some joint swelling. There is limitation of movement and muscle wasting. The complications are: Ruptured tendons, ruptured joints, (baker's cysts), joint infection, spinal cord compression, amyloidosis. It may be seropositive or seronegative for IgM rheumatoid factor.

Fig. 26.1: Rheumatoid arthritis of hands

INITIAL INVESTIGATIONS

Blood count—normochromic, normocytic anemia may be present.

The erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) raised in proportion to the activity of the inflammatory process and are useful in monitoring treatment.

Serology—Anticitrullinated peptide antibodies (ACPA) are present in 80% of people with RA. Positivity for rheumatoid factor (RF) and ACPA is associated with a worse prognosis and an increase in the likelihood of bony erosions. RF is present approximately in 70% cases and antinuclear antibody (ANA) at low titers in 30%.

X-rays show soft tissue swelling in early disease but MRI demonstrates synovitis and early erosions. Aspiration of the joint if an effusion is present, is done.

Doppler ultrasound is an effective way of demonstrating persistent synovitis.

The goals of drug therapy in RA are:

- Ameliorate pain, swelling and joint stiffness.
- Prevent articular cartilage damage and bony erosions.
- Prevent deformity and preserve joint function.

Treatment

1. Non-steroidal Anti-inflammatory Drugs (NSAIDs)

These afford symptomatic relief in pain, swelling, morning stiffness, immobility but do not arrest the disease process, e.g. aspirin, indomethacin, mefenamic acid, ibuprofen, naproxen, meloxicam and diclofenac. NSAIDs cause gastric ulcers, bleeding, perforation in bowel, CVS adverse effects, salt water retention, edema.

2. Non-biological Drugs [Disease Modifying Antirheumatoid Drugs (DMARDS)]

1. Immunosuppressants: Methotrexate, azathioprione and cyclosporine
2. Sulfasalazine
3. Chloroquine or hydroxychloroquine
4. Lefunomide

DMARDs: Methotrexate (Mx) given at low doses exerts potent anti-inflammatory action than as an immunosuppressant. It is a folate antimetabolite that inhibits dihydrofolate reductase, increasing concentration of intracellular adenosine. Adenosine acts through cell surface receptors to inhibit production of inflammatory cytokines. Induction of low dose—7.5 –15 mg weekly. Mx regimen provides onset of symptom relief in 4–6 weeks, therefore preferred for initial treatment. The dose of 25–30 mg weekly can be given lifelong.

- The other DMARDs can be added to methotrexate therapy if there is partial or no response to methotrexate. The most common side-effects observed after methotrexate treatment for RA are mucosal ulceration and nausea. Taking leucovorin–folinic acid once after methotrexate dosing reduces the severity of adverse effects. Periodic liver enzyme tests, complete blood counts and monitoring for signs of infection are recommended.
- Probenecid and aspirin increase methotrexate levels and toxicity. Methotrexate is contraindi cated in pregnancy, breast feeding, liver disease, active infection, leucopenia and peptic ulcer.

- **Azathioprine:** It is a potent suppressant of cell mediated immunity, affects differentiation and function of T cells and natural killer cells. It also has steroid sparing effect for which it is used in cases with systemic manifestations. Dose—50–150 mg/day.

Sulfasalazine: It is a compound of sulfapyridine and 5-aminosalicyclic acid (5-ASA). Sulfapyridine has antibacterial activities and 5-ASA is anti-inflammatory. Efficacy of sulfasalazine in RA is modest and side effects may be unpleasant. Neutropenia/thrombocytopenia occur in 10% patients. It is contraindicated in individuals with hypersensitivity to salicyclates, sulfonylureas and certain diuretics, in pregnancy and lactation. It is used as second-line drug for milder cases or is combined with methotrexate. The dose is 500–1000 mg, 8 hrly/day.

Chloroquine and hydroxychloroquine: These are antimalarial drugs which induce remission 50% of RA in cases but take 3–6 months. Their advantage is low toxicity, possessing modest DMARD activity. The bony erosions are not prevented. They interfere with functioning of lysosomes, inhibit T and B lymphocytes, monocytes and macrophages. For RA, these drugs have to be given for long periods, accumulate in tissues and produce toxicity–retinal damage and corneal opacity. The dose of chloroquine is 150 mg/day.

Hydroxychloroquine: 400 mg/day for 4–6 weeks followed by 200 mg/day for maintenance.

Lefunomide: This immunomodulator inhibits T-cell proliferation and inhibiting tyrosine kinases associated with cytokine and growth factor receptors. Arthritic symptoms are suppressed and radiological progression of disease is retarded. Lefunomide is given in a loading dose of 100 mg daily for 3 days followed by 20 mg OD. It is not to be given in children and pregnant/lactating women. Lefunomide is alternative to methotrexate which can be added to it, but the combination is more hepatotoxic.

3. Biological Agents

1. TNF-α inhibitors—etanercept, infliximab and adalimumab
2. IL1 antagonist—anakinra

IL1 and TNF-α are proinflammatory cytokines involved in the pathogenesis of RA. When secreted by synovial macrophages, IL1 and TNF-α stimulate synovial cells to proliferate and synthesise collagenase, thereby degrading cartilage, stimulating bone resorption and inhibiting proteoglycan synthesis. The TNF-α inhibitors (adalimumab, etanercept and infliximab) have been used to decrease signs and symptoms of RA, reduce progression of structural damage and improve physical function. They are indicated in moderate-to-severe rheumatoid arthritis.

- Clinical response can be seen within 2 weeks of therapy. If patient has failed therapy with one TNF-α inhibitor, a trial with a different TNF-α inhibitor or a non-TNF biologic therapy (abatacept, rituximab, tocilizumab and tafacitinib) is appropriate. Patients receiving TNF-α inhibitors are at increased risk for infections, fungal opportunistic infections, pancytopenia. These agents should be used cautiously in those with heart failure, as they can worsen it.
- Though effective as monotherapy, they are added to methotrexate (Mx) in rapidly progressing cases.
  - ***Etanercept:*** It is recombinant fusion protein of TNF-α receptor and Fc portion of human IgG administered by SC injection, 500 mg subcutaneous weekly. It binds to soluble TNF-α and TNF-β and forms inactive complexes lowering the cytokine levels. It should not be initiated in patients with active infection.

- ***Infliximab:*** It is a chimeral monoclonal antibody which binds and neutralises TNF-α—3–5 mg/kg—300 mg on 0, 2- and 8-weeks IV shots and then infused IV at 4–8 weeks intervals. Susceptibility to respiratory infections is increased and worsening of CHF is noted. Infliximab produces an infusion-related reaction consisting of chills and fever in 20% of patients. Autoantibodies and antibodies to the drug can develop.
- ***Adalimumab:*** This recombinant human IL1 receptor antagonist. Dose is 100 mg SC daily.
- ***Abatacept*** which inhibits T-cell activation and rituximab, a monoclonal antibody that/destroys and depletes B-cells.
- ***Anakinra***—blocks the action of IL1. It is human IL1 antagonist. The most common adverse reactions are redness, bruising, pain and inflammation at the injection site. Dose—10 mg SC daily.
- Corticosteroids have potent immunosuppressive and anti-inflammatory activity, can be induced at any stage in RA along with first line or second line drugs, if potent immunosuppressant action is required while continuing the NSAID + DMARD. They do not arrest the rheumatoid process though joint destruction may be slowed and bony erosions delayed.

Gout and Treatment

It is a disorder of uric acid metabolism characterized clinically by hyperuricemia and recurrent attacks of acute arthritis. Hyperuricemia is defined as a serum urate concentration of >7 mg/dl in males and >6 in females. The first metatarsophalangeal joint is the classical site for gout. Other sites are foot, ankle, knee or hand joints. The attack is acute and starts in night. The joint and surrounding tissues are swollen, red, shiny and extremely painful. In untreated gout over years, sodium urate crystals (tophi) may deposit in subcutaneous tissue, joints, renal parenchyma and renal pelvis (Fig. 26.2). The Herbedens nodes and Bouchard nodes are found usually in palms and soles. The risk factors include alcohol, dietary excesses, surgery,

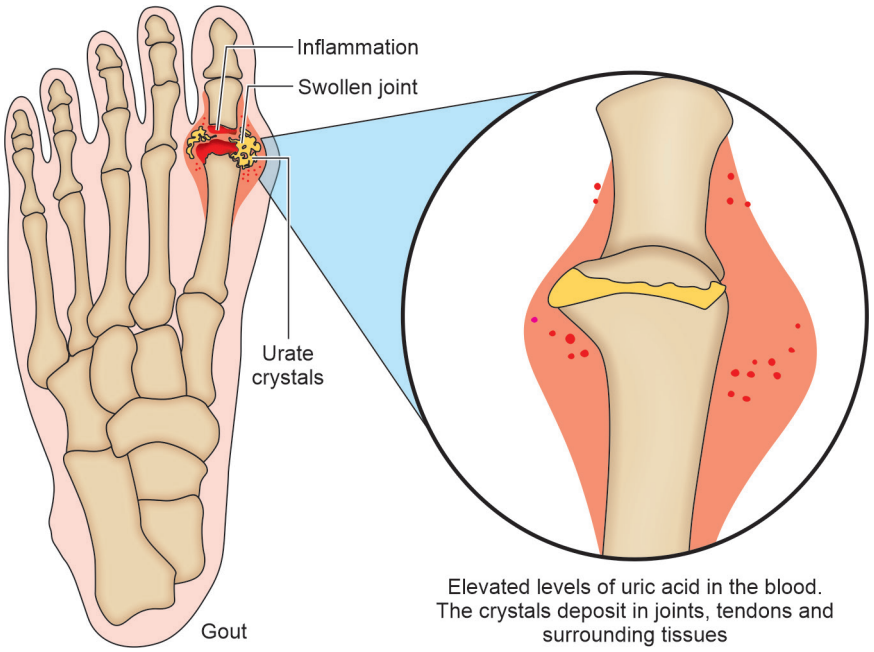
Inflammation
Swollen joint
Urate crystals
Gout
Elevated levels of uric acid in the blood. The crystals deposit in joints, tendons and surrounding tissues

Fig. 26.2: Clinical presenation of gout

trauma, sepsis, stress, starvation, dehydration. It develops more in men than women (10:1). Some 90% of people with gout have impaired excretion of uric acid and 10% have increased production due to high cell turnover and 1% have an inborn error of metabolism.

The overall prevalence of gout is 2–6 per 1000.

CAUSES OF IMPAIRED EXCRETION OF URIC ACID

1. Chronic renal disease
2. Drug therapy—thiazide diuretics, low dose aspirin, pyrazinamide.
3. Hypertension
4. Lead toxicity
5. Primary hyperparathyroidism/hypothyroidism
6. Increased lactic acid production from alcohol, exercise, starvation
7. Glucose-6-phosphatase deficiency

Secondary hyperuricemia occurs in:

- Leukemias, lymphomas, polycythemia when treated with chemotherapy or radiation, due to enhanced nucleic acid metabolism and uric acid production.
- **Drug-induced**—thiazides, furosemide, pyrazinamide, ethambutol, levodopa reduce uric acid excretion by the kidney.

Investigations: Serum uric acid, aspirate fluids—monosodium urate (MSU) crystals from joints and soft tissue.

Drugs used in gout are:

- **For acute gout**—NSAIDs, colchicine, corticosteroids
- For chronic gout
  a. Uricosurics—probenecid, sulfinpyrazone
  b. Synthesis inhibitors—allopurinol, febuxostat

Non-steroidal anti-inflammatory drugs (NSAIDs)—one of the strong antinflammatory drugs, e.g. naproxen, piroxicam, diclofenac, indomethacin or etoricoxib is given in high and quickly repeated doses. They are quite effective in terminating the attack, but may take 12–24 hrs. Naproxen and piroxicam inhibit chemotactic migration of leukocytes into the inflamed joint. After the attack is over, they may be continued at lower doses for 3–4 weeks. Indomethacin and phenylbutazone posess anti-inflammatory, antipyretic, analgesic effects and useful for short term management of acute gouty arthritis. Phenylbutazone is in addition uricosuric.

- **Colchicine:** is a plant alkaloid, used as an anti-inflammatory agent in treatment of acute gouty arthritis. It prevents the release of chemotactic factors and inflammatory cytokines from the neutrophils Colchicine binds leucocyte microtubules causing their depolymerization, decreasing attraction of leukocytes into inflamed area. Furthermore, colchicine blocks cell division by binding to mitotic spindles.
- The relief of pain and inflammation occur within 48 hours.
- **Treatment of acute gout:** Colchicine is the fastest acting drug to control an acute attack of gout. Orally 0.6 mg BD given for 6 months. However, it has high toxicity. Cochicine may cause nausea, abdominal pain and diarrhoea. In overdose, colchicine produces kidney damage, CNS depression, intestinal bleeding. In acute phase, methyl prednisolone can be given, 125 mg IV TDS for a week. Plenty of oral fluids are administered.

- **Chronic gout:** When pain and stiffness persist in a joint between attacks, gout has become chronic. Other cardinal features are hyperuricemia, tophi (in pinna, eyelids, nose, around joints).

Probenecid: Given in sufficient dose, it blocks the active reabsorption of uric acid in the proximal tubules after filtration by glomerules, enhancing its elimination. It promotes uric acid excretion and lowers its blood level. It is used in chronic gout and hyperuricemia, started at 0.25 mg BD and increased to 0.5 mg BD. It gradually lowers blood urate levels. Colchicine/NSAID cover is advised to avoid precipitation of acute gout. Probenecid and other uricosurics are ineffective in the presence of renal insufficiency, patients with blood disorders e.g. leukemia, polycythemia vera. It should not be given with salicyclates as they interfere with the clinical effects of both sulfinpyrazone and probenecid.

Allopurinol: It is xanthine oxidase inhibitor, the enzyme involved in metabolism of hypoxanthine and xanthine to uric acid. It reduces serum urate levels through a competitive inhibition of uric acid synthesis. It is drug of choice in treatment of chronic tophaceous gout and beneficial in patients with renal insufficiency. It is completely absorbed after oral administration. It is well-tolerated by most patients. Skin rashes, gastrointestinal, hepatotoxicity, fever are the most common adverse reactions. Therapy is accompanied with sufficient increase in fluid intake to cause diuresis and by alkalizing urine. The dose is 100 mg OD × 6 months.

Febuxostat is a xanthine oxidase inhibitor. Its adverse effect profile is similar to that of allopurinol although the risk for rash and hypersensitivity reactions is reduced. The dose is 40 mg OD.

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Chapter
27

Treatment of Respiratory Diseases

TREATMENT OF COMMON COLD AND ALLERGIES

Histamine is ubiquitously present in animal tissues and in certain plants, e.g. stinging nettle. Histamine is present mostly within storage granules of mast cells. Tissues rich in histamine are skin, gastric, intestinal mucosa, lungs, liver and placenta.

PHARMACOLOGICAL ACTIONS

Blood vessels: It causes dilation of small blood vessels including arterioles, capillaries and venules. Vasodilation is through H_1 receptor mediated by endothelium dependent relaxing factor (EDRF). Larger arteries and veins are constricted. Intradermal injection causes triple response—red spot, wheal and flare.

- Heart—increases contraction
- Visceral smooth muscle—bronchoconstriction
- Glands—gastric secretion
- Sensory nerve endings—itching
- Autonomic ganglia and medulla—BP increase
- Mediate hypersensitivity reactions. Histamine causes urticaria, angioedema, bronchoconstriction, anaphylaxis.
- As transmitter—initiates sensation of itch and pain at sensory nerve endings.

Mediator of Inflammation

There are 4 types of histaminic receptors—H_1, H_2, H_3, H_4. H_1 receptors cause smooth muscle contraction, H_2 receptors cause gastric acid secretion, H_3 receptors decrease histamine in lungs, brain and skin. H_4 receptors decrease cytokine secretion in prolonged fever.

Antihistaminics are classified as:

First highly sedative—diphenhydramine, dimenhydramine, promethazine, hydroxyzine

Moderately sedative—pheniramine, cyproheptadine, meclizine, cinnarizine, cyclizine

Mild sedative—chlorpheniramine, clemastine

Second generation agents

- Terfenadine
- Desloratidine
- Asmetizole
- Azelastine
- Ebastine
- Loratidine
- Fexofenadine
- Cetrizine
- Mizolastine
- Rupatadine

H_1 blockers—cause antagonism of histamine. They block histamine induced bronchoconstriction, cause contraction of intestinal and other smooth muscle and triple response. They have antiallergic action, prevent motion sickness, have anticholinergic action.

- **First generation H_1 blockers:** They are used in type 1 hypersensitivity reactions and common cold. Promethazine is used in preanesthetic medication and as antiemetic. Cinnarizine (10–15 mg OD) and promethazine are used as antivertigo drugs, prevent entry of calcium into vesicular cells. They cause CNS depression, antiparkinsonian effects, sedation, decreased alertness and concentration, motor incoordination, fatigue and tendency to fall asleep. Dryness of mouth, alteration of bowel movement, urinary hesitancy and blurring of vision can be assigned to anticholinergic activity.
- **Second generation H_1 blockers:** The classical H_1 antihistamines are well-absorbed from oral and parenteral routes, metabolised in liver and excreted in urine. The newer compounds penetrate brain poorly.

They have H_1 selectivity, absence of antidepressant property, no antiemetic effects, do not cross BBB.

Indications are for allergic rhinitis, conjunctivitis, hay fever, pollinosis, urticaria, dermatographism, atopic eczema.

Terfenadine blocks K^+ channels in overdose, produce ventricular tachycardia particularly with erythromycin.

Fexofenadine 120–180 mg oral——should be given in allergic rhinitis. It is active metabolite of terfenadine. It is free of arrythmogenic potential. It causes torsades de pointes occurring with high doses when it is coadministered with CYP3A4 inhibitors (erythromycin, clarithromycin, ketoconazole and itraconazole).

Loratidine is another long-acting peripheral H_1 antagonist which lacks antidepressant effects and is fast-acting. Dose—10 mg oral

Cetrizine inhibits release of histamine and of cytotoxic mediators from platelets and prevents eosinophil chemotaxis during secondary phase of allergic response. Dose—10 mg oral.

Azelastine, this new H_1 blocker has good topical activity, it inhibits histamine release and inflammatory reaction triggered by platelet-activating factor (PAF) and leukotrienes (LTs).

Asmetizole is used for maintenance therapy. It is used for allergic disorders, pruritis, common old, motion sickness, preanesthetic medication, as sedative hypnotic. Dose—4 mg oral.

Uses of H_1 Antihistaminics

- **Allergic disorders:** H_1 antihistaminics block the effect of released histamine, are only palliative.
- **Other conditions involving histamine:** They afford symptomatic relief in insect bite and ivy poisoning.
- **Pruritis:** First choice drugs for idiopathic pruritis,
- **Common cold:** Afford symptomatic relief by anticholinergic and sedative action.

- **Motion sickness:** Pomethazine, diphenhydramine, dimenhydrinate 25–50 mg oral have prophylactic value in milder types of motion sickness, should be taken 1 hour before starting journey.'

MANAGEMENT OF COUGH

Cough is a useful physiological protective mechanism that helps to expel out and clear the respiratory passages from secretions and foreign bodies. Cough serves as a major complaint in almost all patients with pulmonary diseases and in a wide range of extrapulmonary diseases. Most common cause of cough is upper respiratory tract viral infections (Fig. 27.1).

COUGH REFLEX

The cough reflex arc consists of five parts:

1. Cough receptors
2. Afferent nerves
3. Brainstem cough generator circuit
4. Efferent nerves
5. Effector organs (muscles).

Types of Cough

1. Productive cough
2. Nonproductive/dry cough

Common Causes of Cough

- Upper and lower respiratory tract infections
- Allergic rhinitis
- Smoking
- Pulmonary tuberculosis
- Chronic bronchitis
- Interstitial lung disease
- Gastroesophageal reflux disorders (GERDs)
- Drugs (ACE inhibitors, amiodarone, iodides, beta-blockers)
- Asthma

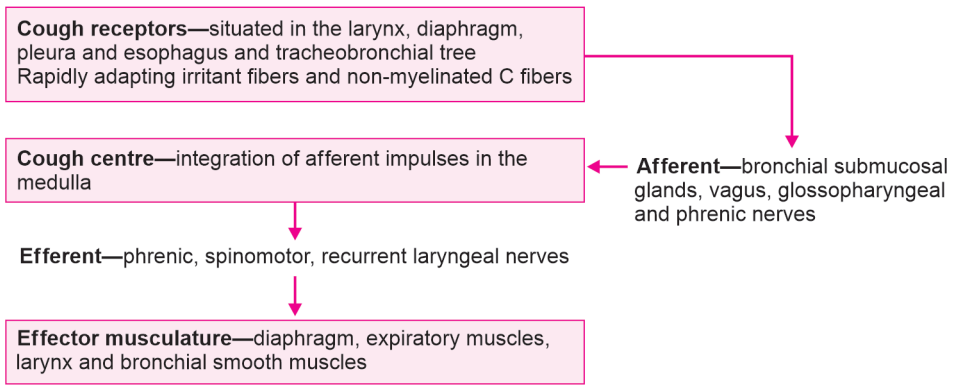

Cough receptors—situated in the larynx, diaphragm, pleura and esophagus and tracheobronchial tree
Rapidly adapting irritant fibers and non-myelinated C fibers
Cough centre—integration of afferent impulses in the medulla
Afferent—bronchial submucosal glands, vagus, glossopharyngeal and phrenic nerves
Efferent—phrenic, spinomotor, recurrent laryngeal nerves
Effector musculature—diaphragm, expiratory muscles, larynx and bronchial smooth muscles

Fig. 27.1: Pathway of cough reflex

- Heart failure
- Pneumonia
- Bronchiectasis

CLASSIFICATION

When cough arises above the larynx, syrups and lozenges that soothingly coat the larynx may be used, e.g. simple linctus. When cough arises below the larynx—warm aerosol inhalations and warm environment may give relief. Certain group of drugs like opioids act at the medullary centre and suppress cough.

1. Antitussives

Pharyngeal demulcents, syrups, lozenges and steam inhalation.

Centrally-acting	*Peripherally-acting*
Opioid mechanism like codeine, pholcodeine, levopropoxyphene	Pharyngeal demulcents, syrups, lozenges and steam inhalation
Non-opioid mechanism like noscapine, dextromethorphan	

2. Expectorants

Directly-acting	*Indirectly-acting*
Guaifenesin, sodium citrate	Ipecac, ammonium salts

3. Mucolytics

Bromhexine, ambroxol, methylcysteine and acetylcysteine

4. Others

Antihistamines, bronchodilators.

1. ANTITUSSIVES

Ideally cough should not be suppressed, and the treatment of the underlying pathology must be the target. Antitussives are cough suppressants.

Mechanism of action: They increase the threshold of cough impulse in the medulla and reduce respiratory tract tussal impulse. Useful in chronic debilitating dry cough.

Centrally-acting

Codeine: Semisynthetic opioid analgesic is less potent than morphine. More selective for the cough centre and act as cough suppressants at lower doses. They are less addictive. The antitussive effect can be reversed by naloxone.

Dose–10 mg BD

Side effects: Drowsiness, constipation, and respiratory depression. Contraindicated in bronchial asthma.

Pholcodeine: Longer-acting derivative of codeine with no addictive or analgesic effect.

Noscapine: Belong to benzylisoquinoline group. They do not impair with mucociliary mechanism.

They are histamine releasing, hence contraindicated in bronchial asthma.

Dose–15 mg BD

Side-effects: Nausea, headache, tremor, bronchoconstriction.

Dextromethorphan: Derivative of methorphan and raise the threshold of cough centre. It is N-methyl-D-aspartate (NMDA) receptor antagonist with least addiction and constipation. They have no analgesic or mucociliary action. Effect cannot be reversed by naloxone.

Dose–10 mg TID

Side-effects: Nausea, vomiting, ataxia.

Peripherally-acting Antitussives

Demulcents, syrups and lozenges sooth the throat and reduce afferent impulses from the inflamed pharyngeal mucosa. Provides symptomatic relief in dry cough.

2. EXPECTORANTS

Mechanism of action: Acts by increasing the volume of secretions in respiratory tract and decreasing its viscosity that may be more easily removed by ciliary action and coughing.

- **Directly-acting:** Directly acting like sodium and potassium citrate or acetate which increases the bronchial secretion by salt action.
- **Indirectly-acting:** Indirectly acting like ipecac and ammonium salt which act as a gastric irritant and reflexively increases the gastric secretion.

3. MUCOLYTICS

Mechanism of action: They have free SH groups that open disulphide bonds in mucus and decrease its viscosity and are given orally or by inhalation, e.g. acetyl cysteine and carbocysteine.

Acetylcysteine itself can cause bronchospasm, hence to be used with caution.

Bromhexine: Synthetic derivative of 'vasaka'.

Causes depolymerisation of mucopolysaccharide, increases the lysosomal activity, increases the volume and decreases the viscosity of sputum.

Adverse effects: GI irritation, lacrimation, rhinorrhea. Used to clear mucus plugs. Ambroxol is a metabolite of bromhexine with similar properties.

Dose–30 mg TID.

Dornase-alfa: Human recombinant DNase that cleaves DNA, given by inhalation used in cystic fibrosis.

4. OTHERS

Antihistamines

Add on to antitussives and expectorants. They have no selectivity to cough centre and do not have any expectorant action. They act by anticholinergic and sedative effect. Suitable for allergic cough, e.g. diphenhydramine, promethazine and chlorphenaramine.

Bronchodilators

They reduce bronchospasm and relieve cough in bronchial asthma, e.g. beta 2-agonists like salbutamol and terbutaline.

Local Anaesthetics

Lignocaine is given as nebulization for intractable cough in malignancy, before bronchoscopy to prevent cough.

Hydration

Adequate hydration decreases the viscosity of secretion and steam inhalation liquifies tenacious sputum.

The definitive treatment of cough lies in treating the underlying disease causing cough.

MANAGEMENT OF BRONCHIAL ASTHMA

Asthma is one of the most common chronic non-communicable disease, affecting over 260 millions people globally characterized by variable respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough, and variable expiratory airflow limitation. It is usually associated with airway inflammation. People with asthma often have periods of worsening symptoms and worsening airway obstruction, called exacerbations (also called attacks or flare-ups), that can be fatal.

PATHOGENESIS OF ASTHMA

Asthma is characterized by inflammation of airways from trachea to the terminal bronchioles characterized by recruitment of mast cells, macrophages, dendritic cells, eosinophils, neutrophils and T-lymphocytes (Table 27.1 and Fig. 27.2).

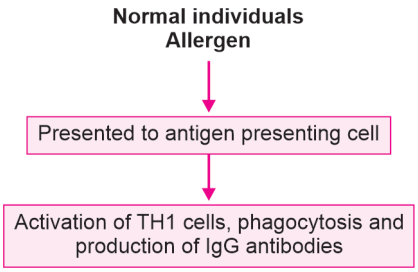
Table 27.1: Inflammatory mediators in asthma

Mediators	*Actions*
Histamine, PGD2	Prostaglandin D2, cysteinyl leukotriene mediates smooth muscle constriction, microvascular leakage, increased mucus secretion, chemoattractant for inflammatory cells.
Cytokines	IL4, IL5, IL13—allergic inflammation IL1beta, TNF—alpha-amplify inflammation Thymic stromal lymphopoietin (TSLP)—nitric oxide chemoattractant for TH2 cells
Nitric oxide	Act as a relaxant, causes vasodilatation
LTD4	Bronchoconstriction Mucus hypersecretion and capillary leakage Called slow reacting substance of anaphylaxis

Pathophysiology

The hallmark of the disease is:

- Airway hyper-responsiveness
- Inflammation of bronchial walls
- Increased mucus secretion


Normal individuals
Allergen
Presented to antigen presenting cell
Activation of TH1 cells, phagocytosis and production of IgG antibodies

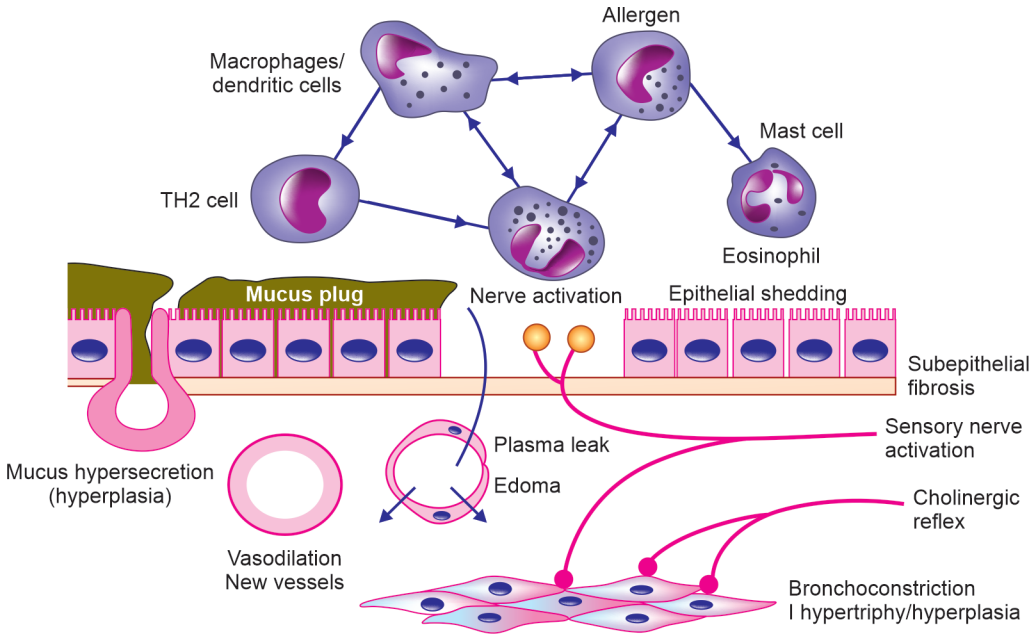


Fig. 27.2: Pathogenesis of bronchial asthma

DRUGS IN ASTHMA (Fig. 27.3)

Controllers: Control/treat chronic inflammation, prevent future attacks and prevent airway remodeling (Fig. 27.4).

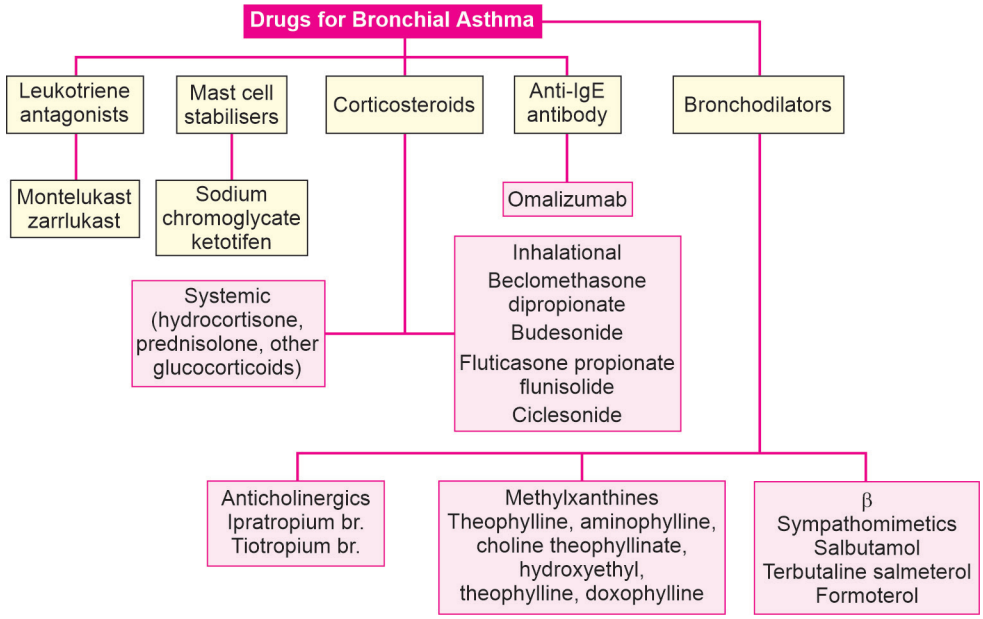


Fig. 27.3: Drugs in asthma

Relievers	Controllers
• Rapidly-acting beta 2-agonists • Methylxanthines—immediate release • Anticholinergics	• Steroids • Mast cell stabilisers • Antileukotrienes • Biologicals • Long-acting beta 2-agonists

Fig. 27.4: Releivers and controllers of asthma

CLASSIFICATION OF DRUGS

1. SYMPATHOMIMETICS (SYMPATHETIC BETA-AGONISTS) (Table 27.2)

Table 27.2: Sympathetic beta-agonists

Non-selective	*Selective (beta 2-agonist)*
Epinephrine	Salbutamol
Ephedrine	Terbutaline
Isoprenaline	Salmeterol, formoterol
Orciprenaline	Bambuterol, indacaterol, oladaterol

Beta 2-Agonists—mechanism of Action (Figs 27.5 and 27.6)

- Increased cyclic AMP in bronchial smooth muscles and cause relaxation of smooth muscles and decrease the release of inflammatory mediators.
- Increased conductance of large calcium sensitive potassium channels leading to membrane hyperpolarization and relaxation.

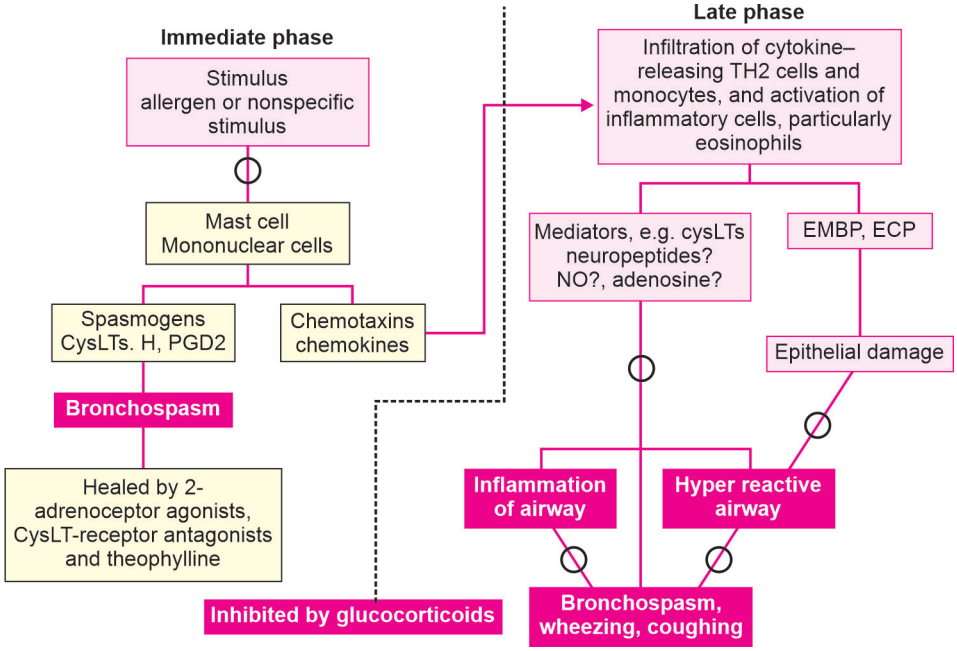


Fig. 27.5: Action of drugs

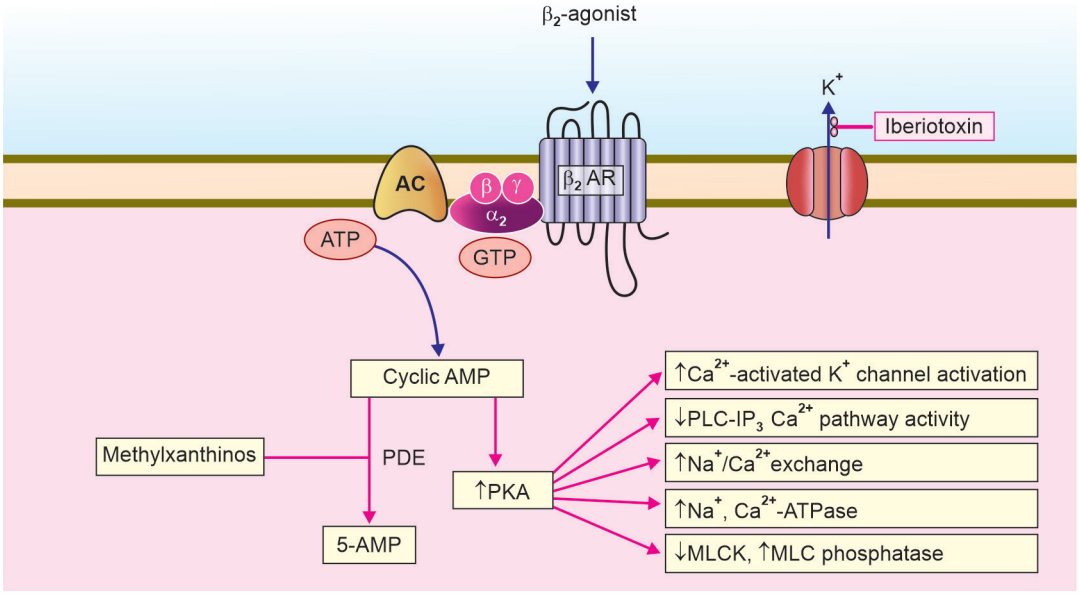


Fig. 27.6: Stimulation of beta 2-receptors

Receptor Desensitisation

Chronic stimulation of the receptors in inflammatory cells will lead to rapid desensitisation. Hence, beta 2-agonist has a little role in preventing airway inflammation. While the receptors on the bronchial smooth muscles are resistant.

Classification of Beta Agonist Based on Duration of Action

- **Short-acting beta-agonist (SABA):** Onset of action in 5 minutes, last for 4 to 6 hours, hence drug of choice for acute attacks, e.g. Salbutamol, terbutaline, Pirbuterol, Levosalbutamol, Fenoterol, Metaproterenol.
- **Long-acting beta-agonist (LABA):** Duration of action is 12 hours hence twice daily dose given for prophylaxis, e.g. salmeterol, formoterol.
- **Ultra LABA:** Duration of action is for 24 hours. Once daily dose can be used for prophylaxis of asthma, e.g. indacaterol.

Short-acting beta 2-agonists: For symptom relief and acute bronchodilation (Table 27.3).

Table 27.3: Short-acting beta-agonists

1. Salbutamol	• Used in acute attack of asthma/COPD • Inhaled dose—100 to 200 µg 4 to 6 hourly • Oral—2 to 4 mg 6 to 8 hourly • Nebulized dose—2.5 mg 6 to 8 hourly • Side-effects—tremors due to receptor stimulation in skeletal muscle – Palpitation – Ankle oedema – Hypo or hyper – Kalemia, hyperglycemia

Contd.

Table 27.3: Short-acting beta-agonists	
2. Levosalbutamol	• R enantiomer of salbutamol • More potent bronchodilator • Lesser side-effects, hence safe in patients with arrythmia • Inhaled dose—0.63 to 1.25 mg • Available as metered dose inhaler, nebulization
3. Terbutaline	• Same as salbutamol • Oral—5 mg • SC—0.25 mg • Inhalation—250 µg
4. Metaproteronol	• Available as 650 µg inhaler • Less beta 2 selective • More prone to cardiac stimulation
5. Pirbuterol	• Inhalation 400 µg 4 to 6 hourly

Long-acting Beta 2 Adrenergic Agonist (LABA) (Table 27.4)

- Derived by bulky substitution in aliphatic chain, moderately lipophilic
- Formoterol and salmeterol >12 hours used for both asthma and COPD.
- Formoterol has faster onset of action and has additive effect when used in asthma.

Ultralong Acting

- Indacaterol, oladaterol, vilanterol
  - – Currently approved only for the treatment of COPD
- LABA causes pronged bronchodilation, useful for the management of exercise induced bronchospasm and nocturnal episodic asthma.
- Should never be used alone in asthma, should always be combined with inhalational corticosteroids (ICS) to treat the underlying inflammation
- Adverse effects: Alters serum electrolytes increasing the risk of arrythmia
  - – Tremor, tachycardia, palpitation, headache
- Only bronchodilator safe in pregnancy is terbutaline

Table 27.4: Long-acting beta agonists	
Formoterol	• Used in asthma as adjunctive to ICS • Maintenance and treatment of severe COPD • Fast onset of action • Inhaled 12 to 24 µg two times daily • Nebulised 20 µg in 2 ml 12th hourly
Arformoterol	• Arformeterol—maintenance drug in severe COPD
Salmeterol	• Nebulized 15 µg/2 ml BD—salmeterol, inhaled 50 to 100 µg BD
Indacaterol	• Indacaterol—75 µg OD
Olodaterol	• Olodaterol—2.5 µg OD

2. ANTICHOLINERGICS OR ANTIMUSCURANICS

Mainly act on large airways and block the bronchoconstrictor tone. Usually, combined with beta 2-agonists in treating acute severe asthma. Act on M3>M1 receptors. They include (Table 27.5):

Table 27.5: Anticholinergics		
Ipratropium bromide Albuterol (salbutamol)/ipratropium combination	• Inhaled, 2 puffs (17 µg/puff) 3–4 times/day • Combination albuterol 103 µg/ipratropium 18 µg/puff; 2 puffs 4 times daily	• Replaced by LABAs • Avoid spraying in eyes • Adverse effects include dry mouth, tachycardia, urinary retention, glaucoma • Combination with albuterol may be used as a reliever
Tiotropium bromide	2.5 µg via oral inhalation (2 puffs of 1.25 µg/actuation) once daily	• Caution in patients with urinary retention or glaucoma history
Umeclidinium bromide	(DPI) 62.5 µg (1 puff) inhaled once daily	
Aclidinium bromide	(DPI) 400 µg (1 puff) inhaled twice daily DPI-dry powder Inhaler	

3. METHYL XANTHINES

Theophylline (Mechanism of action)

Exact mechanism is unknown: Likely mechanisms are the following:

1. Act by inhibiting phosphodiesterase involved in breaking of cAMP, resulting in accumulation of cyclic AMP and GMP.
   - Effect is minimal in therapeutic range
2. **Adenosine receptor antagonism:** Adenosine is a potent bronchoconstrictor. Side-effect—cardiac arrythmia, seizures.
3. **IL10 release:** IL-10 is anti-inflammatory and reduced in asthma.
4. **Effects on gene transcription:** Prevents the translocation of proinflammatory transcription factor, **NF-κb** into the nucleus, hence reducing the expression of inflammatory genes.
5. **Effects on apoptosis:** Reduces apoptosis, hence prolonged survival of eosinophils and neutrophils.
6. **Histone deacetylase activation:** Switch off the inflammatory genes.

Side Effects

Nausea, headache, GI disturbance due to PDE4 inhibition, diuresis and seizures due to adenosine antagonism, arrythmias due to PDE3 and adenosine antagonism.

Dose–8 mg/kg BD orally

- Theophylline has a low therapeutic index, hence titration must be done to maintain plasma levels 5–15 mg/litre.
- Aminophylline can be used with a loading dose of 6 mg/kg followed by 0.5 mg/kg/hour for acute attack of asthma.
- Doxophylline is long acting, lesser side effects. Dose is 400 mg OD.

4. CORTICOSTEROIDS

Not a bronchodilator: Used in inflammatory lung diseases. All corticosteroids are active when given systemically (prednisolone, prednisone and dexamethasone). Substituting 17 alfa-ester position improves topical absorption, e.g. beclomethasone, triamcinolone and

flunisolide. Use of inhaled corticosteroids have helped to reduce the dose of oral steroids, hence reducing its side effects.

Mechanism of Action

- Reduces eosinophils and mast cells in the airways.
- Reduces activated T-lymphocytes.
- **Activate anti-inflammatory genes:** Mitogen activated protein kinase phosphatase 1.
- Increased expression of beta 2-receptors.

Synergism between Steroids and α2-Agonists

Steroids increase the transcription of beta 2-gene in the airway mucosa and prevent the downregulation of beta 2-receptors. Beta 2-agonist enhance the binding of glucocorticoid receptors to the DNA and increase its translocation to the nucleus.

Classification of Drugs (Tables 27.6 and 27.7)

Table 27.6: Maintenance treatment for asthma—inhaled corticosteroids

Beclomethasone dipropionate (BDP)	• Orally bioavailable BDP Beclomethasone Monopropionate • Systemic effects: Growth suppression. Bruising, adrenal suppression
Fluticasone propionate Budesonide	• Lesser systemic effects than BDP • Used in children less than 8 who cannot use PDI
Ciclesonide	• Minimal systemic effects of all ICSs • Maybe effective once daily

Table 27.7: Short course or oral maintenance for asthma (and COPD)

Prednisone, prednisolone	• Oral: 40–80 mg once daily or divided dose for 3–10 days for acute exacerbation • Minimal dose for maintenance	• Prednisone converted to prednisolone in the liver • Bruising, weight gain exacerbation, edema, osteoporosis, diabetes, cataracts, adrenal suppression
Hydrocortisone succinate	IM/IV: 100–500 mg every 12 hrs for acute severe asthma	• Only if patient not able to take oral streoids

Side-Effects

Local

- Dysphonia
- Oropharyngeal candidiasis
- Cough

Systemic

- Adrenal suppression and insufficiency
- Bruising
- Cataract
- Growth suppression
- Osteoporosis
- Glaucoma

- Metabolic abnormalities
- Secondary infection
- Psychiatric disturbances

5. MAST CELL STABILISER

Include sodium cromoglycate, nedocromil sodium and ketotifen.

Mechanism of Action

Stabilizes mast cell and inhibits degranulation of mast cells and other inflammatory cells. Decreases bronchial hyperreactivity.

- Nedocromyl is more effective, dose is 4 mg QID approved in those more than 12 years.
- Ketotifen has additional antihistamine action, dose is 1–2 mg BD in adults. S/E-sedation.

6. ANTILEUKOTRIENES (Fig. 27.6)

- Orally administered as a maintenance therapy.
- Used in aspirin induced asthma.
- Montelukast and Zafirlukast competitively prevent bronchoconstrictor effects of cysteinyl leukotrienes.
- Montelukast is given 10 mg OD and Zafirlukast 20 mg BD.
- Zileuton is 5 lipo-oxygenase inhibitor, S/E-Zileuton-Hepatotoxic

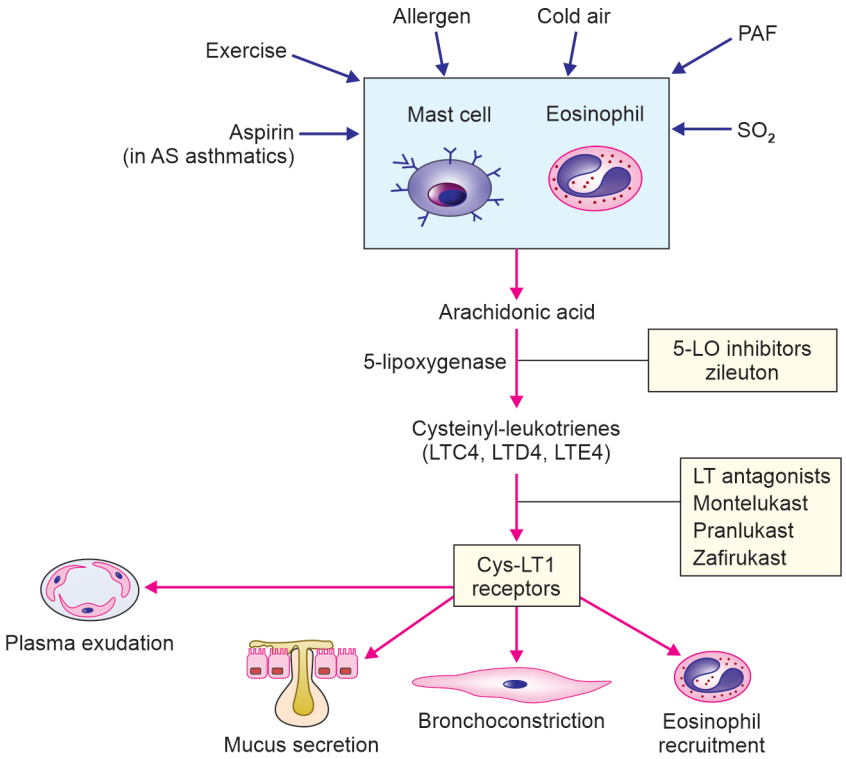


Fig. 27.7: Mechanism of action of antileukotrienes

7. BIOLOGICALS (Table 27.8)

Table 27.8: Use of biologicals in asthma

Anti-IgE (Omalizumab, SC ≥6 years)	An adjunctive for patients with severe allergic asthma uncontrolled on high dose ICS-LABA	Minor reactions at the site of injection are common Anaphylaxis is rare
Anti-IL5 and anti-IL5R (Anti-IL5 mepolizumab SC, ≥12 years) or reslizumab [IV, ≥18 years], or anti-IL5 receptor benralizumab [SC, ≥12 years]	Adjunctive for patients with severe eosinophilic asthma uncontrolled on high dose ICS-LABA. For SC injection, self-administration may be permitted	Headache and reactions at injection site are common but minor
Anti-IL4R (Dupilumab, SC, ≥12 years)	Adjunctive for patients with severe eosinophilic or type 2 asthma uncontrolled on high dose ICS-LABA or requiring maintenance OCS.	Minor reactions at injection sire are common, blood eosinophilia occurs in 4 to 13% of patients

Current Management of Asthma (Figs 27.8 and 27.9)

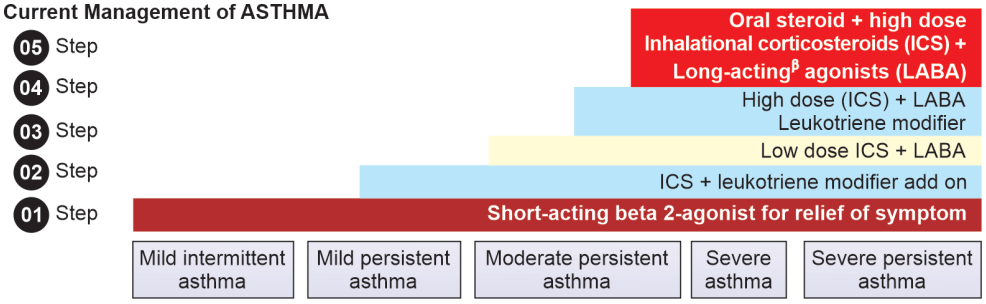

Current Management of ASTHMA
05 Step
04 Step
03 Step
02 Step
01 Step
Oral steroid + high dose Inhalational corticosteroids (ICS) + Long-acting$^{\beta}$ agonists (LABA)
High dose (ICS) + LABA Leukotriene modifier
Low dose ICS + LABA
ICS + leukotriene modifier add on
Short-acting beta 2-agonist for relief of symptom
Mild intermittent asthma
Mild persistent asthma
Moderate persistent asthma
Severe asthma
Severe persistent asthma

Fig. 27.8

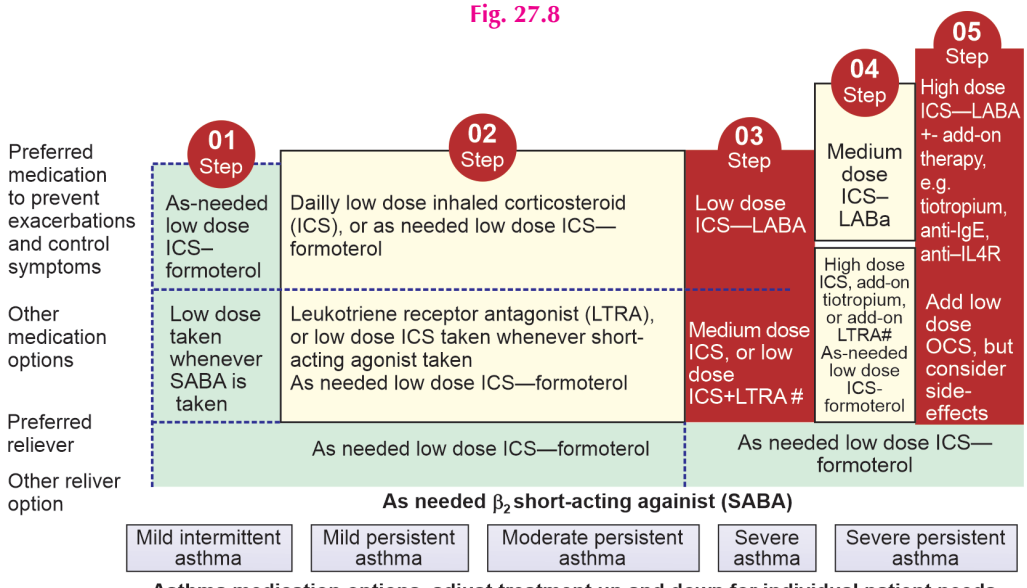

01 Step
02 Step
03 Step
04 Step
05 Step
Preferred medication to prevent exacerbations and control symptoms
Other medication options
Preferred reliever
Other reliver option
As-needed low dose ICS–formoterol
Dailly low dose inhaled corticosteroid (ICS), or as needed low dose ICS—formoterol
Low dose ICS—LABA
Medium dose ICS–LABa
High dose ICS—LABA +- add-on therapy, e.g. tiotropium, anti-IgE, anti–IL4R
Low dose taken whenever SABA is taken
Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever short-acting agonist taken
As needed low dose ICS—formoterol
Medium dose ICS, or low dose ICS+LTRA #
High dose ICS, add-on tiotropium, or add-on LTRA# As-needed low dose ICS-formoterol
Add low dose OCS, but consider side-effects
As needed low dose ICS—formoterol
As needed low dose ICS—formoterol
As needed β_2 short-acting againist (SABA)
Mild intermittent asthma
Mild persistent asthma
Moderate persistent asthma
Severe asthma
Severe persistent asthma
Asthma medication options, adjust treatment up and down for individual patient needs

Fig. 27.9

Newer Agents

- Selective glucocorticoid receptor agonist (SEGRA), e.g. mapracorat, dabrocorat.
- PDE4 inhibitors—roflumilast, cilomilast
- Gold COPD guidelines 2023.

Aerosol delivery devices predominantly involves 3 classifications: Small-volume nebulizer (SVN), pressurized metered-dose inhaler (pMDI), and dry powder inhaler (DPI). They provide ways to deliver medication directly to the respiratory tract and decreases the systemic absorption.

Status Asthmaticus

It is a medical emergency. It is extreme form of asthma marked by hypoxemia, hypercarbia and secondary respiratory failure. Treatment is by:

- Hydrocortisone hemisuccinate—100 mg IV stat followed by 100 mg 8 hourly infusion.
- Nebulize with salbutamol (2.5–5 mg) + ipratropium bromide 0.5 mg.
- High flow humidified O_2 inhalation
- Salbutamol/terbutaline 0.4 mg IM/SC to reach smaller bronchi.
- Intubation and mechanical ventilation if required.
- Antibiotics to treat or prevent chest infection.
- Saline + sodium bicarbonate infusion to correct dehydration and acidosis.

MANAGEMENT OF PNEUMONIA

Community Acquired Pneumonia

Acute infection of pulmonary parenchyma, where the infection has been acquired from the community.

Classification of Illness

Disease is classified into 3 categories based on the following parameters:

- Confusion
- Urea (blood urea nitrogen in the United States) >7 mmol/L (20 mg/dl)
- Respiratory rate ≥30 breaths/minute
- Blood pressure (BP; systolic <90 mmHg or diastolic ≥60 mmHg)
- Age ≥65 years

Each of the parameter is assigned a score of 0 if absent and 1 if present.

Table 27.9: Prognosis of community acquired pneumonia

Curb 65 score	*Risk of mortality in 30 days (%)*	*Where to manage*
0–1	1.5	HOME
2	9.2	IP
3–5	22	HDU/ICU

Treatment

1. Treatment of pneumonia in OPD basis in a patient with no comorbidities

Beta-lactams, e.g. tablet amoxicillin 500 mg to 1 gram, TID, 3 to 7 days

OR

Macrolides, e.g. tablet azithromycin 500 mg OD

Fig. 27.10: (a) Nebuliser; (b) mouth piece for nebulization; (c) rotahaler; (d) ultrasonic nebulizer; (e) i, ii Breath actuated meter dose inhaler (f) MDI with dose counter

In cases of allergy to beta-lactams and macrolide resistance, oral doxycycline 100 mg, BD can be used as an alternative.

2. Treatment of pneumonia in OPD basis in a patient with comorbidities

Oral combination therapy is recommended. Beta-lactams with macrolides for 5 to 7 days.

3. Treatment of inpatient non-ICU patients

The recommended regimen is combination of a β-lactam plus a macrolide (preferred β-lactams include ceftriaxone, cefotaxime, and amoxicillin clavulanic acid).

In case of beta-lactam hypersensitivity, it can be replaced by a fluroquinolone monotherapy after ruling out tuberculosis. In admitted patient, initially IV route is preferred to increase absorption of the drug. Once the patient clinically improves, they can be switched on to oral therapy for 5 to 7-day duration.

4. Treatment of inpatient ICU patients (severe pneumonia)

- Beta-lactam plus macrolide is recommended in all patients whom *Pseudomonas* is not suspected.

- In case of suspected pseudomonas, an antipneumococcal, antipseudomonal agent should be considered (e.g. cefepime, ceftazidime, cefoperazone, piperacillin—tazobactam, cefoperazone sulbactam, imipenem, or meropenem).
- Combination therapy with respiratory fluroquinolones or aminoglycosides can be considered.
- In cases of suspected methicillin-resistant *Staphylococcus aureus* (MRSA), add anti MRSA agent like linezolid, teicoplanin or vancomycin.

RISK FACTORS FOR PNEUMONIA

Table 27.10: Risk factors for MRSA and *pseudomonas*

MRSA	*Pseudomonas*
• Colonization of known MRSA • Infection of prior MRSA • Prior MRSA • In the prior 3 months prior MRSA • Use of IV antibiotics • Recent influenza-like illness • Necrotizing or cavitary pneumonia • Empyema • Immunosuppression Risk factors for MRSA colonization, including: End-stage kidney disease Crowded living conditions (e.g. incarceration) Injection drug use Contact sports participation	• Known *Pseudomonas* • Colonization • Prior *Pseudomonas* infection • Recent antibiotic use of any kind • Frequent COPD exacerbations requiring glucocorticoid and/or antibiotic use • Other structural lung diseases (e.g. bronchiectasis, cystic fibrosis)

HOSPITAL ACQUIRED PNEUMONIA

Pneumonia that occurs 48 hours or more after admission and did not appear to be incubating at the time of admission.

A. If the patient has severe pneumonia, is in septic shock or needs mechanical ventilation or if the patient has received IV antibiotics in the last 90 days or has a high risk of Gram negative infection and methicillin-resistant *Staphylococcus aureus* (MRSA), patient must receive a combination of antipseudomonal drugs plus anti MRSA in addition to a respiratory fluroquinolone or aminoglycoside.

Antipseudomonal drugs:

- Piperacillin-tazobactam, 4.5 g IV, every 6 hours
- Cefepime, 2 g IV, every 8 hours
- Ceftazidime, 2 g IV, every 8 hours
- Imipenem, 500 mg IV, every 6 hours
- Meropenem, 1 g IV, every 8 hours
- Aztreonam, 2 g IV, every 8 hours

Respiratory fluroquinolone or aminoglycoside

- Amikacin, 15 to 20 mg/kg IV, daily
- Gentamicin, 5 to 7 mg/kg IV, daily

- Tobramycin, 5 to 7 mg/kg IV, daily
- Levofloxacin or ciprofloxacin

MRSA coverage

- Vancomycin/telavancin/linezolid

B. If the patient has no risk factors for MRSA or Gram-negative bacilli, no use of IV antibiotics in the last 90 days and not in shock, then he can be empirically started on injection PIPTAZ or cefepime or levofloxacin.

C. In a hospital set up, where there is MRSA prevalence more than 20%, HAP should be treated with antipseudomonal and an anti-MRSA.

PHARMACOLOGICAL MANAGEMENT OF INTERSTITIAL LUNG DISEASES (ILDs)

Interstitial lung diseases (ILDs) are a group of rare respiratory, nonmalignant disorders, characterized by varying degrees of damage to the lung parenchyma via inflammation and fibrosis.

Treatment of Progressive Fibrosing ILD

Antifibrotics: Nintedanib and pirfenidone

Nintedanib: Oral intracellular tyrosine kinase inhibitor. It inhibits the pathway involved in fibrogenesis. It binds to the ATP-binding domain of tyrosine kinase receptors and inhibits the activation of platelet derived growth factor, fibroblast, and vascular endothelial growth factor. These are responsible for the growth and proliferation of fibroblast which get halted. This drug was approved in 2014 after INPULSIS 1 and 2 and TOMORROW trial. These trials showed that nintedanib decreases the annual rate of fall in FVC. The dose is 150 mg BD. Most common side-effect is diarrhea and transaminitis.

Pirfenidone: Anti-inflammatory drug with antiproliferative and antioxidant properties. Approved based on the results of CAPACITY1 and 2 and ASCEND trial. The recommended daily dose is 267 mg capsules thrice daily. Initially, started with one tab thrice daily for a week, followed by 2 tabs thrice daily for a week reaching the therapeutic dose in 14 days. Side-effects are photosensitivity, liver enzyme disturbances.

Management of Connective Tissue Disease Related ILD

CTD-ILD showing non-specific interstitial pneumonia (NSIP) pattern can be managed with steroids with or without immunosuppressants. In refractory cases, second-line immunosuppressants like cyclophosphamide is used. Biological agents like rituximab have been also tried.

The definitive treatment for progressive fibrosing ILD is lung transplantation.

PHARMACOLOGICAL MANAGEMENT OF BRONCHIECTASIS

Most effective method of treatment for bronchiectasis is chest physiotherapy, however pharmacological management is also useful in acute exacerbation of bronchiectasis and bacterial colonization. Antibiotic therapy is important in bronchiectasis exacerbation to decrease the bacterial load and reduces airway and systemic inflammatory properties. Acute exacerbation can be caused by bacteria, virus and fungal infections, hence antibiotics, antivirals and antifungals, will help in control of acute exacerbation.

ANTIBIOTICS IN BRONCHIECTASIS

Fluroquinolones: Levofloxacin, ciprofloxacin can be used in bronchiectasis patients

i. Without sputum culture report
ii. β-lactamase positive organism
iii. Sensitive pseudomonas infection

Macrolides: Azithromycin, clarithromycin in

i. β-lactamase sensitive organism
ii. Long-term antibiotics

Long-Term Antibiotics (≥3 Months) (BTS)

Long-term antibiotics in bronchiectasis indicated if patient had three or more exacerbation in last one year, it depends upon colonization by *Pseudomonas* bacterial infection.

Table 27.11: Antibiotic treatment in bronchiectasis

	Pseudomonas colonized patients	*Non-P. aeruginosa colonised patients*
First-line drug	Inhaled colistin	Azithromycin (250 mg thrice weekly) or erythromycin
Second-line drug	Inhaled gentamicin	Inhaled gentamicin
Alternative	Azithromycin (250 mg thrice weekly) or erythromycin	Doxycycline

Long-term inhaled antibiotics showed a reduction of the sputum bacterial density (P <0.00001) and augmented eradication of sputum *P. aeruginosa* (P <0.00001).

Bronchodilators

Beta-agonist and long-acting anticholinergic can be used for breathlessness management but no randomized trial on bronchiectasis patient.

But in patients with COPD or asthma co-existing bronchiectasis should follow the guideline recommendations for COPD or asthma.

Anti-inflammatory Therapy in Bronchiectasis

Inhaled corticosteroids may be used as anti-inflammatory as it reduces sputum volume in bronchiectasis but associated with local and systemic side effects. But there was a limited evidence to evaluate the role of oral corticosteroids, PDE4 inhibitors, methylxanthines or leukotriene receptor antagonists in bronchiectasis.

ACID–BASE DISORDERS

Primary management of acid–base disorders lies in identifying the etiology and treating the cause.

Respiratory acidosis—is characterized by an increase in PCO_2 and decrease in pH. Oxygen must be given to correct acute hypoxia. Hypercapnia needs to be managed with positive pressure ventilation based on indication. Management lies in treating and identifying cause.

Respiratory alkalosis—is characterized by an increase in pH and decrease in PCO_2. Renal compensation would reduce the plasma bicarbonate concentration. The treatment of underlying cause corrects respiratory alkalosis. Rebreathing bag may allow CO_2 retention and correction of acid–base abnormality.

Metabolic acidosis—is characterized by decrease in pH and reduction in bicarbonate concentration. It is compensated by a reduction in PCO_2. The underlying metabolic acidosis should be treated, e.g. withdrawal of toxic substances, treatment of hyperglycemia, fluid and electrolyte imbalance.

- In diabetic ketoacidosis insulin therapy will enhance ketoacid utilization with bicarbonate regeneration and correction of acidosis.
- Alcoholic ketoacidosis—responds to glucose and saline infusions and alkalis if pH <7.1.
- Proximal tubular acidosis—by sodium restriction, contraction of the extracellular fluid resets the glomerulotubular balance upwards and raises the fractional rate of sodium and bicarbonate reabsorption by the proximal tubule.
- Methyl alcohol; administration of ethyl alcohol is useful.
- Dialysis whenever the acidosis is severe and uncorrected by large doses of alkalis, hemodialysis or peritoneal dialysis must be done.

Metabolic alkalosis—is characterized by increase in pH and an increase in bicarbonate and slight elevation of PCO_2.

Treatment is with IV or oral sodium chloride and potassium chloride which suppresses acid excretion and promotes bicarbonate excretion.

Potassium is useful in hyperaldosteronism as potassium reverses the intercellular shift of hydrogen ions and enhances bicarbonate excretion.

Spironolactone: In hyperaldosteronism, the drug acts as physiological antagonist.
Acetazolamide: In edematous states, increases excretion of bicarbonates.

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Chapter
28

Pulmonary Function Tests

SPIROMETRY

Spirometry is the most common pulmonary function test. It is commonly used in the assessment of lung function to provide objective information used in the diagnosis of lung diseases and monitoring lung health.

Spirometry Indication/Uses

- Diagnose the presence or absence of lung disease
- Evaluate disability or impairment
- Assess risk for surgical procedures
- Quantify the extent of known disease on lung function
- Determine beneficial or negative effects of therapy
- Measure effects of occupational or environmental exposure
- Epidemiologic or clinical research involving lung health or disease

Contraindications

Increases in myocardial demand or changes in blood pressure intraocular pressure	*Increases in intracranial/middle ear pressures*	*Increases in sinus and intra-abdominal pressure*	*Increases in intrathoracic pressure*	*Infection control issues*
1. Acute myocardial infarction within 1 week 2. Systemic hypotension or severe hypertension 3. Significant atrial/ventricular arrhythmia 4. Non-compensated heart failure 5. Uncontrolled pulmonary hypertension 6. Acute cor pulmonale	1. Cerebral aneurysm 2. Brain surgery within 4 weeks 3. Recent concussion with continuing symptoms 4. Eye surgery within 1 week	1. Sinus surgery or middle ear surgery or infection within 1 week	1. Presence of pneumothorax 2. Thoracic surgery within 4 weeks 3. Abdominal surgery within 4 weeks 4. Late-term pregnancy	1. Active or suspected transmissible respirratory or systemic infection, including tuberculosis 2. Physical conditions predisposing to the transmission of infections, such as hemoptysis, significant secretions, oral lesions, or oral bleeding

Increases in myocardial demand or changes in blood pressure intraocular pressure	*Increases in intracranial/middle ear pressures*	*Increases in sinus and intra-abdominal pressure*	*Increases in intrathoracic pressure*	*Infection control issues*
7. Clinically unstable pulmonary embolism 8. History of syncope related to forced expiration/cough				

Procedure

Pre-test instructions:

- Smoking and/or vaping and/or water pipe used within 1 hour before testing should be avoided
- Restrict vigorous exercise within 1 hours before testing
- Avoid the following medications 6 hours before the test
  1. Albuterol and ipratropium
  2. Ipratropium
  3. Levalbuterol
- Avoid the following medications 12 hours before the test.
  1. Formoterol
  2. Salmeterol
- Avoid the following medication 24 hours before the test.
  1. Tiotropium
- Avoid wearing clothing that substantially restricts full chest and abdominal expansion

STEPS IN PROCEDURE

1. Wash hands
2. Prepare the patient
   - Dispense hand sanitizer for the patient
   - Confirm patient identification, age, birth sex, ethnicity, etc.
   - Measure weight and height without shoes
3. Instruct and demonstrate the test
   - Position of the mouthpiece and nose clip
   - Correct posture with head slightly elevated
   - Inspire rapidly until full
   - Expire with maximal effort until empty
   - Inspire with maximal effort until full
   - Confirm that patient understands the instructions and is willing to comply
4. Perform maneuvre (Fig. 28.1)
   - Have patient assume the correct posture
   - Attach nose clip, place a mouthpiece in the mouth, and close lips around the mouthpiece

- Breathe normally
- Inspire completely and rapidly with a pause of <2 s at TLC
- Expire with maximal effort until no more air can be expelled while maintaining an upright posture
- Inspire with maximal effort until completely full
- Repeat instructions as necessary, coaching vigorously
- Repeat for a minimum of three maneuvers, usually no more than eight for adults
- Check FEV1 and FVC repeatability and perform more maneuvers as necessary.

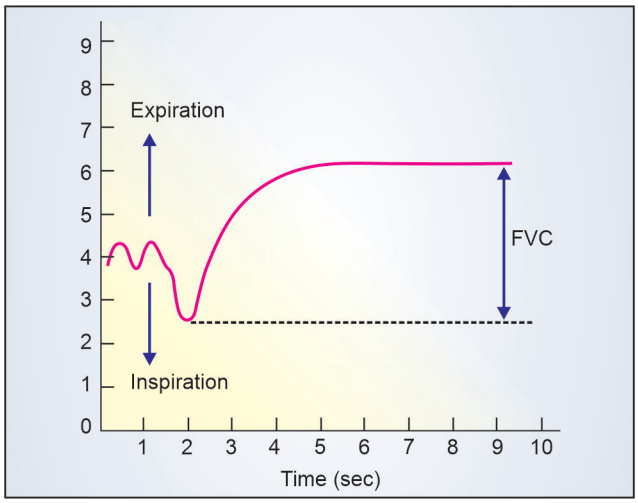


Fig. 28.1: Volume–time curve for spirometry

ACCEPTABILITY CRITERIA

- Freedom from artifacts (coughing, glottic closure, early termination leak, variable effort)
- Good starts (i.e. the initial portion of the curve that is most dependent on patient effort is free from artifact).
- Satisfactory expiratory time (at least 6 seconds of expiration on the volume time curve, or at least 1-second plateau in the volume time curve).

Repeatability Criteria

Once the minimum of three acceptable flow-volume loops has been obtained, the reproducibility of the PFTs should be assessed.

- **Age >6 years:** The difference between the two largest FVC values must be <0.150 L, and the difference between the two largest FEV1 values must be <0.150 L.
- **Age <6 years:** The difference between the two largest FVC values must be <0.100 L or 10% of the highest value, whichever is greater, and the difference between the two largest FEV1 values must be <0.100 L or 10% of the highest value, whichever is greater.

NORMAL SPIROMETRY

Normal PFTs are defined by a normal-shaped flow-volume loop: (Figs 28.2 and 28.3)

- Forced vital capacity (FVC) is defined as the maximum volume of air that is forcefully exhaled after a maximum inspiration.
- Forced expiratory volume (FEV1) is defined as the maximum volume of air exhaled during the first second of the FVC.
- The measured values for FEV1 and FVC are compared to the predicted values for FEV1 and FVC as a percent of predicted. Values of 80–120% are considered normal
- Total lung capacity (TLC) is defined as the volume of air in the lung after complete maximal inspiration and a value of 80–120% of predicted is normal.
- RV is defined as the volume of air left in the lungs after complete maximal expiration and a value of 80–120% of predicted is normal.
- Slow vital capacity (SVC) is defined as the maximal volume of air that can be exhaled with normal effort after a maximum inspiration. (It is similar to the FVC except performed without full force.) A value of 80–120% of predicted is normal.

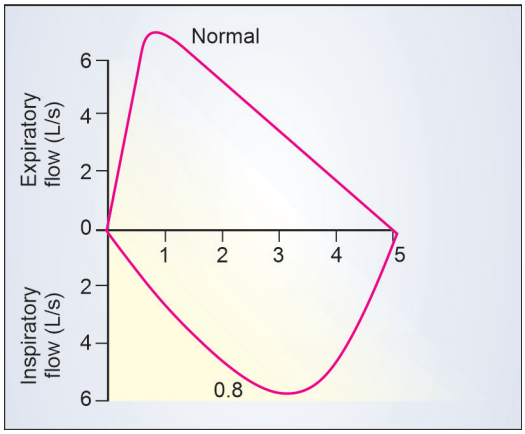


Fig. 28.2: Normal flow volume loop

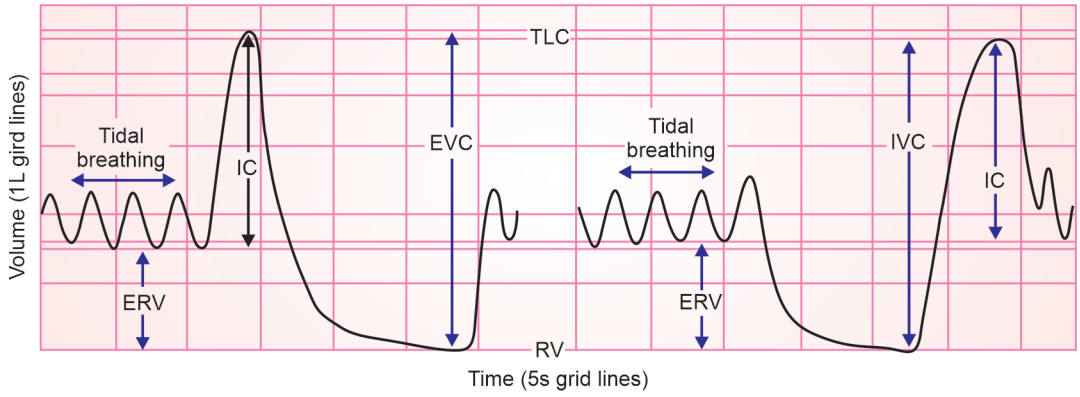


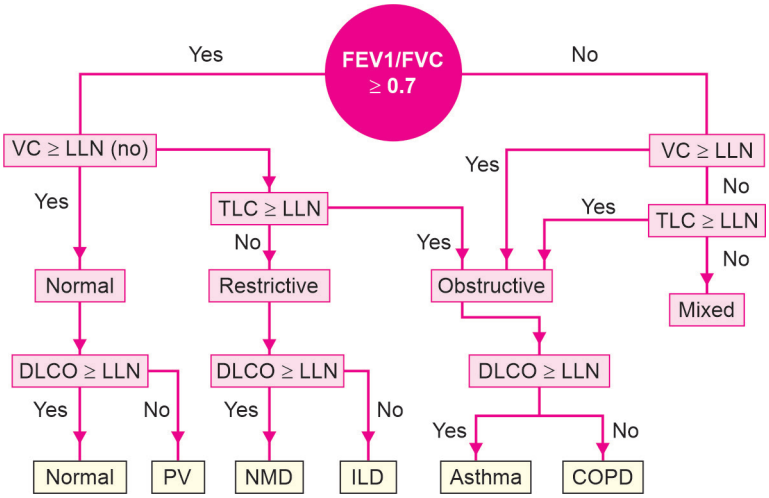
Fig. 28.3: Volume–time curve with various volumes and capacity

ERV = Expiratory reserve volume; EVC = Expiratory VC; IC = Inspiratory capacity; IVC = Inspiratory VC; RV = Residual volume

Peak flow meter—is a portable, inexpensive, handheld device that measures one's ability to push air out of lungs. Air flow is measured by the amount of air blown out in one fast blast (Fig. 28.4).

Fig. 28.4: Peakflow meter

Pulmonary Function Test (Fig. 28.5)



TLC: Total lung capacity, VC: Vital capacity, LLN: Lower limit of normal, PV: Pulmonary vascular disease, NMD: Neuromuscular disease, ILD: Interstitial lung disease, COPD: Chronic obstructive pulmonary disease, DLCO: Diffusion lung capacity for CO.

Fig. 28.5: Approach to pulmonary function test

Bronchodilator Responsiveness Testing

This test is used to determine the degree of improvement of airflow in response to bronchodilator administration (Fig. 28.6).

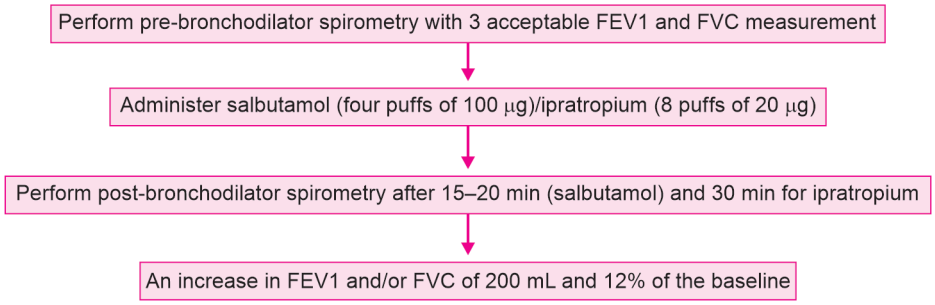

Perform pre-bronchodilator spirometry with 3 acceptable FEV1 and FVC measurement
Administer salbutamol (four puffs of 100 μg)/ipratropium (8 puffs of 20 μg)
Perform post-bronchodilator spirometry after 15–20 min (salbutamol) and 30 min for ipratropium
An increase in FEV1 and/or FVC of 200 mL and 12% of the baseline

Fig. 28.6: Bronchodilator reversibility

DIFFUSING LUNG CAPACITY FOR CARBON MONOXIDE (DLCO)

It is also called transfer factor for carbon monoxide (TLCO), which is used to measure the ability of the lungs to transfer gas from inhaled air to the red blood cells in pulmonary capillaries (Fig. 28.8).

Determinants of Diffusion Capacity (Fig. 28.7)

- Area
- Thickness
- Driving pressure
- Flow
- Area of the RBC membrane
- Coupling of CO with Hb.

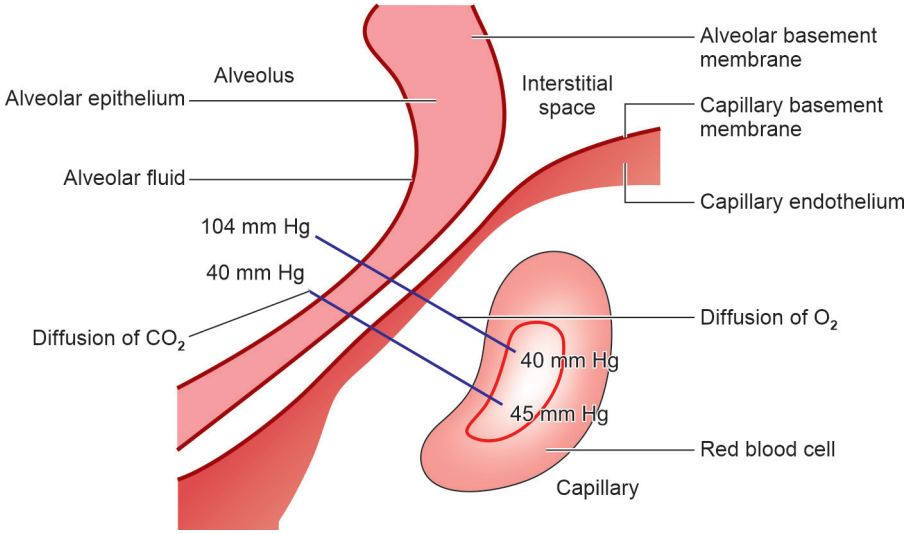


Fig. 28.7: Alveo capillary membrane

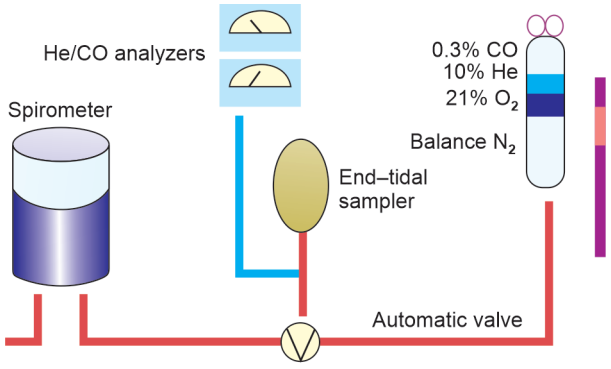


Fig. 28.8: Working diagram of single-breath DLCO equipment

DLCO formula:

$DLCO = VCO/(P_aCO–P_cCO)$

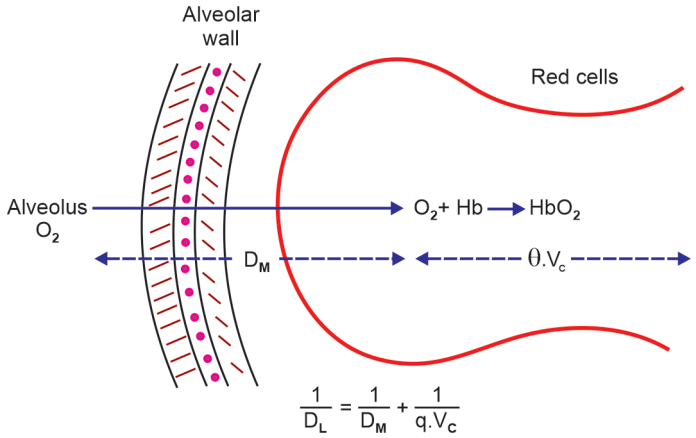
Diffusing capacity = Net rate of gas transfer (ml/min)/Partial pressure gradient (mmHg)

Diffusing capacity influenced by structural and functional factors

Structural Factors	***Functional Factors***
1. Lung gas volume 2. Thickness and area of the alveolar capillary membrane 3. Volume of hemoglobin in capillaries supplying ventilated alveoli	1. Ventilation perfusion ratio 2. Composition of alveolar gas 3. Difusion characteristics of the membrane 4. Concentration and binding properties of hemoglobin in the alveolar capillaries 5. CO_2 and O_2 in the alveolar capillary

The process of carbon monoxide transfer from the environment to the pulmonary capillary blood (Fig. 28.9):

- Bulk-flow delivery of carbon monoxide to the airways and alveolar spaces;



D_L: Diffusion capacity of carbon monoxide, D_M: Diffusion conductance, q: Reaction rate, V_c: Capillary blood volume

Fig. 28.9: Factors determining diffusion capacity of carbon monoxide

- Mixing and diffusion of carbon monoxide in the alveolar ducts, air sacs, and alveoli;
- Transfer of carbon monoxide across the gaseous to the liquid interface of the alveolar membrane;
- Mixing and diffusion of carbon monoxide in the lung parenchyma and alveolar-capillary plasma;
- Diffusion across the red-cell membrane and within the interior of the red blood cell, and
- Chemical reaction with constituents of blood Hb.

Terminologies (ERS/ATS)

- **DLCO:** A measure of the conductance of gas transfer from inspired gas to the red blood cells.
- **VA:** The number of contributing alveolar units and is measured during the single-breath DLCO by use of a tracer gas (e.g. helium).
- **VCO:** Volume of gas per unit time
- **PACO:** Alveolar pressure of carbon monoxide
- **KCO (DLCO/VA):** Index of the efficiency of alveolar transfer of carbon monoxide.
- **kCO (the permeability factor):** Rate constant for alveolar-capillary CO transfer.

Indications

- Evaluation of dyspnea or hypoxemia
- **Screening:** Early ILD
  - Emphysema
  - Pulmonary vascular disease
  - Occupational and drug-induced lung disease
- Follow-up
- Severity assessment (COPD/ILD)
- Preoperative assessment (<20% of predicted)
- Pulmonary disability/impairment evaluation (below 40% predicted–total disability)
- Need for oxygen therapy

Methods

- Single breath-holding method
- Single expiration method
- Rebreathing method
- Steady-state method
- Riley-Lilienthal method

GASES USED IN DLCO (Fig. 28.10)

- **Tracer gas:** Helium
  - Methane
  - Neon
- CO–0.3%
- **Balance gas:** O_2 and nitrogen.

Carbon Monoxide is used in DLCO because of the following reasons:

- Follows the same pathway as oxygen
- Easy to measure in lab settings

- Rapidly absorbable
- Cheap and easily available
- Non-toxic at low level

Normal DLCO: 25 ml/min/mmHg

Grading of DLCO:

High	>140%, predicted
Normal	76–140%, predicted
Mild decrease	61–75%, predicted
Moderate decrease	40–60%, predicted
Severe decrease	<40%

PROCEDURE

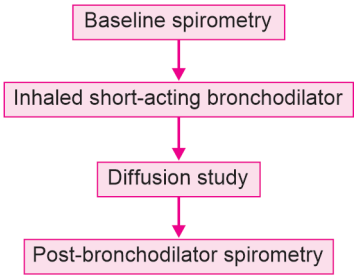


Fig. 28.10: Sequence of doing DLCO and spirometry

CLINICAL SIGNIFICANCE OF DLCO

Increased DLCO (>140%)

1. Recruitment of blood in the alveolar–capillary bed
- Hyperdynamic circulation (exercise and fever)
- Bronchial asthma
- Muller maneuver (inhaling against a closed glottis)
- Cardiac
- Left to right shunt–early congestive heart failure

2. Miscellaneous
- Alveolar hemorrhage
- Obesity
- High altitude
- Following bronchodilators in obstructive airways diseases (OAD) (6%)
- Incorrect reference values

Low DLCO (75%)

1. Decreased surface area
- Pulmonary resection
- Emphysema
- V/Q mismatch (significant bronchial obstruction)

2. Alveolo-capillary membrane disease
- ILD
- Pulmonary vascular disease (PHT, PE)

3. Diffuse alveolar filling
- Late CHF (pulmonary edema fluid impairs gas transfer)
- Diffuse consolidation
- Alveolar proteinosis

LUNG VOLUME

INDICATIONS FOR LUNG VOLUME DETERMINATION

- Diagnose or assess the severity of restrictive lung disease (reduced TLC)
- Differentiate between obstructive and restrictive disease patterns
- Assess response to therapeutic interventions—(1) bronchodilators, steroids, (2) lung transplantation, resection, reduction, (3) radiation or chemotherapy
- Make pre-operative assessments of patients with compromised lung function
- Determine the extent of hyperinflation
- Assess gas trapping by comparison of plethysmographic lung volumes with gas dilution lung volumes. Standardize other lung function measures (i.e. specific conductance).

The most important lung volumes for this discussion are total lung capacity (TLC), residual volume (RV), and slow vital capacity (SVC).

METHODS USED FOR LUNG VOLUME DETERMINATION

Most commonly used methods for static compliance measurement:

1. Body plethysmography (body box), most accurate and widely used
2. Nitrogen washout method
3. Inert gas dilution technique
4. Radiographic method

1. Body Plethysmography

The most common method used to determine the lung volume (Fig. 28.11)

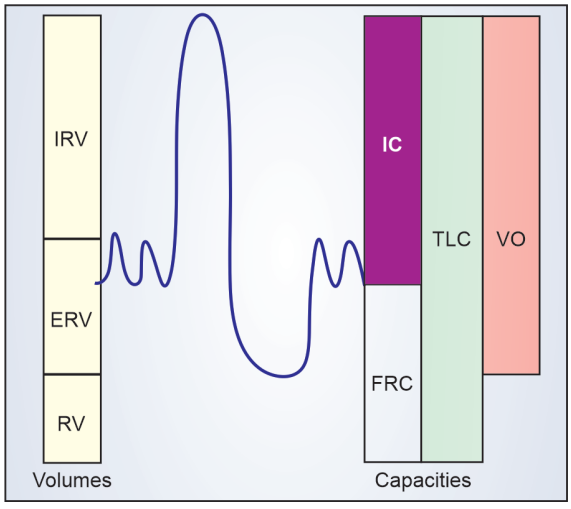


Fig. 28.11: Volumes and capacities

Preparation for Body Plethysmography

1. Avoid smoke at least 1 hour before
2. Avoid alcohol at least 4 hours before the procedure
3. Avoid heavy exercise at least 30 minutes before the procedure
4. Avoid large meal 2 hours before the procedure

Comparison between plethysmography and other methods

Plethysmography	*N_2 washout method/Inert gasdilution technique*
1. Fast 2. Readily repeatable for reproducibility 3. More accurate 4. Expensive, large size and complex 5. Difficult to test patients on wheelchairs or stretchers or patients attached to IV pumps 6. Slightly over-estimates FRC in obstructive disorders	1. Time consuming 2. Difficult to repeat. The test is too long (more time is required for the lungs to equilibrate and to clear inert gas in the dilution technique) 3. Less accurate 4. Cheaper equipment 5. Possible to test patients on wheelchairs or stretchers 6. Under-estimates FRC in obstructive disorders

Body plethysmograph determines the volume of intrathoracic gas measured when airflow occlusion occurs at end-expiration (FRC) during shutter closure.

This technique is based on **Boyle's law** relating pressure to volume.

Closed-circuit (He dilution) determination of FRC. At the beginning of the test, the patient's lungs contain no He. The spirometer contains a known concentration of He in a known volume (Fig. 28.8). The patient then rebreathes the He mixture from this system. He is diluted until equilibrium is reached. At the end of the test, the known volume of He has been diluted in the rebreathing system and the lungs. FRC is calculated from the change in He concentration and the known system volume. The patient must be switched from breathing air to the He mixture at the end-expiratory level for accurate measurement of FRC.

FRC— functional residual capacity of lungs (the volume left in the lungs after normal expiration).

ARTERIAL BLOOD GAS

- Arterial blood gas (ABG) refers to the measurement of pH and the partial pressures of oxygen (O_2) and carbon dioxide (CO_2) in arterial blood.
- From these values, we can assess the state of acid–base balance in the blood and how well the lungs are performing their job of gas exchange.

Uses

- Establish diagnosis
- Assess illness severity
- Guide and monitor treatment

Precautions before the Procedure

- Confirm the need for the ABG and identify any contraindications
- Record details of O_2 therapy and respiratory support
- Explain to the patient about indications and complications.
- Prepare the necessary equipment.

ABG sample is mostly taken from radial artery, less commonly from the femoral and brachial artery.

ABG Sampling Technique

Allen test: To check the patency of the ulnar and radial artery (Fig. 28.12).

Steps: Radial artery sampling

1. Perform the Allen test to assess the adequacy of collateral circulation of the ulnar artery.
2. Extend the wrist around 20–30°. The greater extension will impede the arterial flow.
3. By palpation identify the radial artery.
4. Clean the sampling site and prepare syringe flushed with heparin.
5. Insert the needle at 45° with bevel faced upwards.
6. Flush of pulsatile blood will appear if the needle is in the artery.
7. Obtain at least 3 ml of blood before withdrawing the needle.

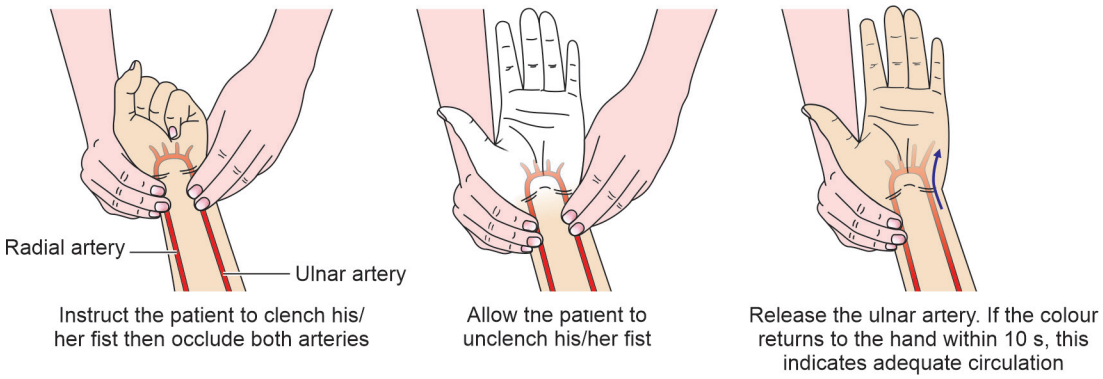

Radial artery
Ulnar artery
Instruct the patient to clench his/her fist then occlude both arteries
Allow the patient to unclench his/her fist
Release the ulnar artery. If the colour returns to the hand within 10 s, this indicates adequate circulation

Fig. 28.12: Modified Allen's test. The modified Allen's test assesses collateral circulation for the hand. A positive test demonstrates adequate collateral circulation and the radial artery may be used for taking blood sample for ABG analysis.

Variables analyzed by Arterial blood gas analysis:

- **Measured values:** pH, PCO_2, PO_2
- **Calculated values:** Oxygen saturation (O_2 sat), HCO_3, base excess (BE)
- ABG machines can also measure electrolytes.

Normal ABG Values

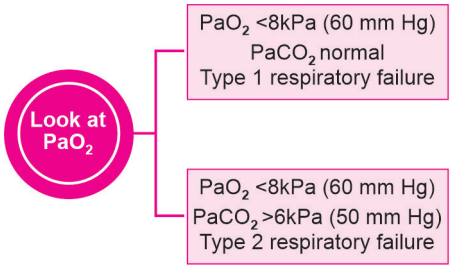
Value	*Normal*	*Abnormal*	
pH	7.35–7.45	<7.35 acidosis	>7.45 alkalosis
PaO_2	>90 mm Hg	75–89 mm Hg, mild hypoxia	<75 mm Hg, severe hypoxia
$PaCO_2$	35–45 mm Hg	<35 mm Hg, alkalosis	>45 mm Hg, acidosis
HCO_3	18–24 m Eq/L	<18 m Eq/L acidosis	>24 m Eq/L alkalosis

STEPS OF ABG ANALYSIS (Fig. 28.13)

Step 0: Is this ABG authentic?
Step 1: Acidosis or alkalosis?

Step 2: Respiratory or metabolic?
Step 3: If respiratory, acute, or chronic?
Step 4: Is compensation adequate?
Step 5: If metabolic anion gap?
Step 6: Check "gap gap" ratio
Step 7: If anion gap normal, urine anion gap
Step 1: ABG authentication calculated by subtracting the last two digits of the pH (e.g. 20 in pH 7.20) from 80; this value is approximately equal to the H^+ concentration.

Look at PaO_2



Look at pH

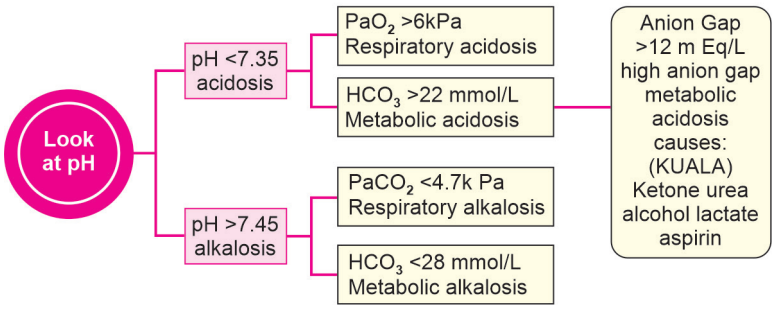


Fig. 28.13: Stepwise approach to ABG interpretation

Compensation Calculation

Disorder	*pH*	*Primary change*	*Compensatory change*	*Equation*
Metabolic acidosis	↓	$(HCO_3^-)\downarrow$	$PCO_2\downarrow$	$\Delta PCO_2 = 1.2 \times \Delta HCO_3$
Metabolic alkalosis	↑	$(HCO_3^-)\uparrow$	$PCO_2\uparrow$	$\Delta PCO_2 = 0.7 \times \Delta HCO_3$
Respiratory acidosis	↓	$(PaCO_2)\uparrow$	$(HCO_3)\uparrow$	Acute $\Delta HCO_3 = 0.1 \times \Delta PCO_2$ Chronic $\Delta HCO_3 = 0.3 \times \Delta PCO_2$
Respiratory alkalosis	↑	$PaCO_2\downarrow$	$(HCO_3)\downarrow$	Acute $\Delta HCO_3 = 0.2 \times \Delta PCO_2$ Chronic $\Delta HCO_3 = 0.5 \times \Delta PCO_2$

If a high anion gap is present, measure delta ratio:

D Ratio = (Anion gap-12)/(24-HCO_3)
If D ratio is >2—metabolic alkalosis
<1—normal anion gap metabolic acidosis
1–2—high anion gap metabolic acidosis

If the anion gap is normal measure the urine anion gap:

Urine anion gap = (Urinary sodium + Urinary potassium)–Urinary chloride

Renal causes like renal tubular acidosis and Addison disease will cause positive urinary anion gap, gastrointestinal causes like diarrhea, villous adenoma, and fistula will produce negative urine anion gap.

Causes of Normal Anion Gap Metabolic Acidosis

'URAD'

U: Ureterosigmoidostomy
R: Renal tubular acidosis
A: Addison disease, ammonium chloride poisoning
D: Diarrhea, lactate poisoning

Causes of High Anion Gap Metabolic Acidosis

'GOLD MARK'

G: Glycol poisoning
O: Oxoproline poisoning
L: Lactic acidosis
D: D Lactate poisoning
M: Methanol poisoning
A: Aspirin
R: Renal failure
K: Ketoacidosis

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Chapter
29

Treatment of Diarrhea, Constipation and Vomiting

DRUGS FOR DIARRHEA AND CONSTIPATION

Increased gut motility and reduced fluid absorption causes diarrhea.

Diarrhea is defined as change in bowel frequency which is more than usual. However, in clinical, practice, we see watery stools with frequency of more than 3 times per day, which at times can be accompanied with blood. Management is crucial at early stage to avoid water loss in body and its subsequent complications.

- Diarrhea can be defined as acute if duration is less than 2 weeks or chronic if duration is more than 4 weeks. It is defined by WHO as 3 or more watery stools in a 24 hour period (Fig. 29.1). In pathological terms, it occurs due to passage of excess water in faeces. This may be due to—
  - Reduced absorption of fluid and electrolytes
  - Increased secretion of fluids from lumen of intestines
  - Increased osmotic content in gut
  - Inflammation of mucosa and loss of fluids into limen.

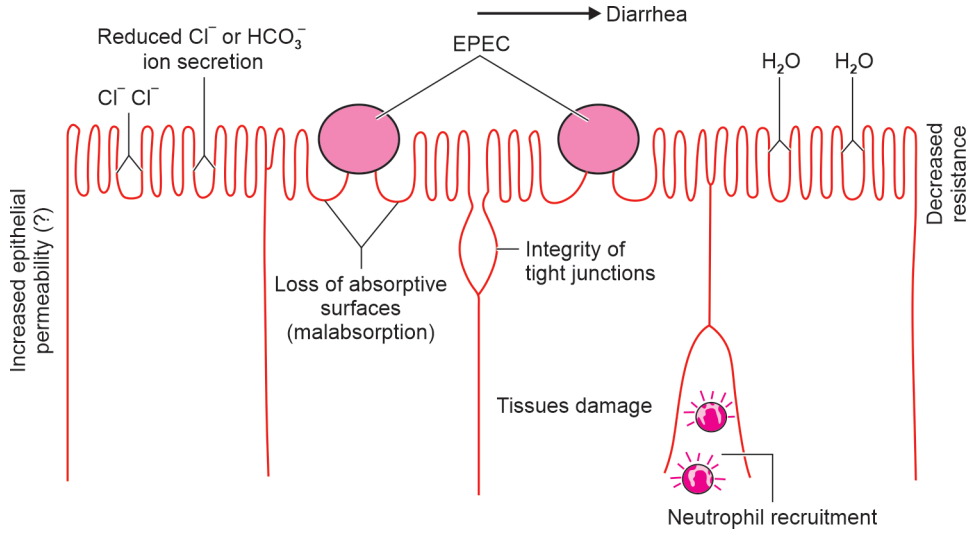

Fig. 29.1: Mechanism of diarrhoea

MECHANISM OF DIARRHEA

- Human intestine absorbs and secretes large quantities of water, minerals, protein, carbohydrates, fats, essential and non-essential food materials. While gastrointestinal secretions from small intestine forms the majority, small proportion comes from oral intake. Diarrhea is the result of a disruption in the delicate balance between the absorptive and secretory processes within the bowel. Diarrhea has been described as either osmotic or secretory.
- **Osmotic diarrhea:** Excess osmotically active particles in the gut lumen. Stops when person is fasting.
- **Secretory diarrhea:** Bowel mucosa secretes excess water into the lumen. Continues even during the fasting state.

The movement of fluid between the intestinal lumen and blood is driven by the active transport of ions, mainly Na^+, Cl^-, HCO_3^-, and K^+, and solutes, mainly glucose. Fluid absorption or secretion involves the coordinated activity of membrane transporters located on the apical (lumen facing) and basolateral (circulation-facing) epithelial membranes. The intestinal epithelium is structurally configured into long, finger-like projections (villi) and glandular, tube-like structures (crypts). Functionally, both absorption and secretion can occur in the same epithelial cells, although secretory processes predominate in crypts and absorptive processes in villi (Fig. 29.2).

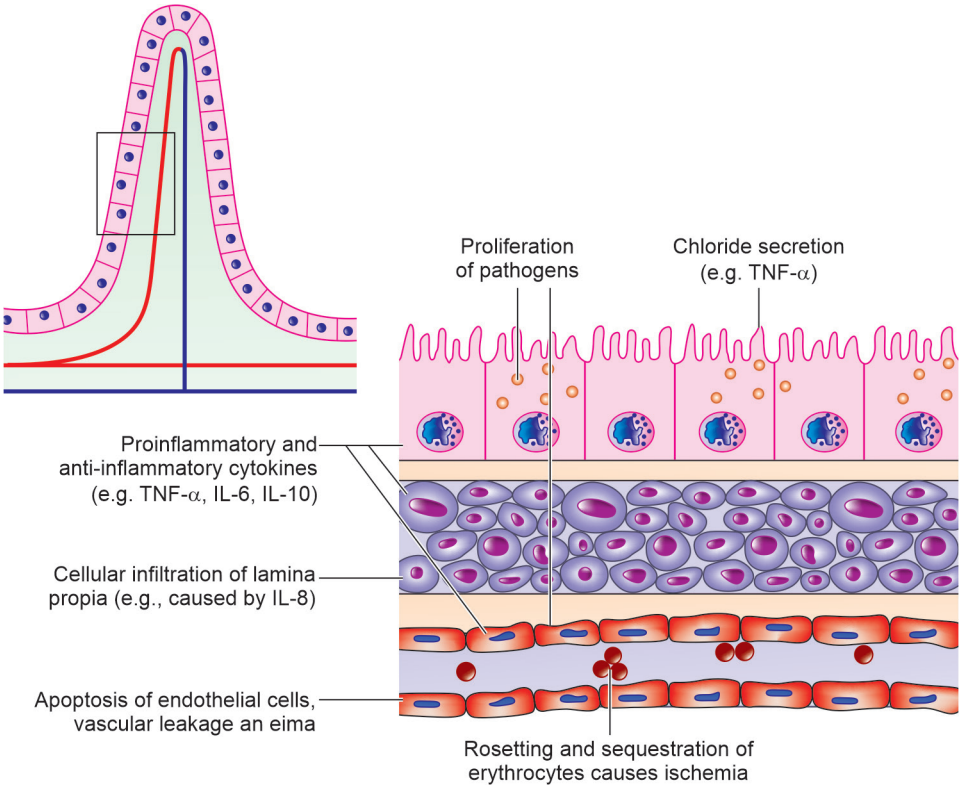
Proliferation of pathogens
Chloride secretion (e.g. TNF-α)
Proinflammatory and anti-inflammatory cytokines (e.g. TNF-α, IL-6, IL-10)
Cellular infiltration of lamina propia (e.g., caused by IL-8)
Apoptosis of endothelial cells, vascular leakage an eima
Rosetting and sequestration of erythrocytes causes ischemia

Fig. 29.2: Pathophysiology of diarrhoea

Anti-diarrheal drugs include antimotility agents, adsorbants and drugs that modify fluid and electrolyte transport.

Pathophysiology: Diarrhoea occurs due to poor absorption of fluids and nutrients in the gut or less commonly from increased secretion of gut mucosa, in the latter called, secretory diarrhea.

PRINCIPLES OF MANAGEMENT

- Management of fluid loss, shock and acidosis.
- Maintain nutrition
- Drugs as needed.

A. Antimotility drugs: Drugs commonly used are diphenoxylate 5–10 mg, loperamide 2 mg, codeine 60 mg TDS. They have opioid-like actions on the gut, activate opioid receptors in enteric nervous system to inhibit acetylcholine release and decrease peristalsis. They diminish intestinal secretions while enhancing absorption. The δ-receptors promote absorption and inhibit secretion while μ-receptors enhance absorption and decrease propulsive movements allowing more time for absorption. They can be used to induce short-term constipation, e.g. after anal surgery and to recuce volume, fluidity and bag cleaning frequency in ileostomy/colostomy patients.

Side effects are drowsiness, abdominal, cramps, dizziness.

These drugs can cause toxic megacolon, avoid usage in young children or patients with severe colitis. They are used in non-infectious diseases, mild travellers' diarrhea, idiopathic diarrhea in AIDS.

B. Adsorbants: Adsorbant agents such as kaolin, pectin, charcoal are used to control diarrhea. They act by inhibiting intestinal toxins or by coating/protecting the intestinal mucosa. These agents cause constipation, they can also interfere with the absorption of drugs.

C. Bulk forming agents: Ispaghula and methylcellulose, agar-agar are used for diarrhea as they decrease the fluidity of feces because they absorb water and swell up modifying consistency and frequency of stools.

D. Oral rehydration solution (ORS): All patients with simple watery diarrhea are given ORS to replace fluid and electrolyte balance.

E. Octreotide: Somatostatin is 14th amino acid peptide released in GIT and pancreas from paracrine cells, D cells and enteric nervous system as well as from hypothalamus. It inhibits intestinal secretion of hormones and transmitters, decreases intestinal secretion and pancreatic secretion, decreases gut motility. It is given IV or subcutaneously or IM.

Clinical uses: Vipomas and carcinoid tumors, diarrhea due to vagotomy/dumping syndrome. Adverse effects are steatorrhea leading to fat soluble vitamin deficiency, alteration in GIT motility—diarrhea, nausea, flatulence, abdominal pain, formation of gallstones, hyperglycemia, hypothyroidism. 50–100 μg SC BD.

F. Antibiotics: These can be used in cases with infectious diarrhea. History and clinical features will suggest if diarrhea is infective. Presence of abdominal cramps, blood in stools, fever will suggest infective etiology.

G. Antisecretory drugs—e.g. racecadotril prevent degradation of endogenous enkephalins (ENK) by mainly δ-opioid receptor agonists—enhance ENK action—lower mucosal cAMP. Indicated in short-term treatment of acute secretory diarrheas. 100 mg TDS for maximum 7 days.

In Traveller's diarrhea, treatment is done with loperamide 2 mg tab initially then given every 4–6 hourly as needed. Additionally, a single dose of ciprofloxacin 750 mg or levofloxacin 500 mg relieves mild cases of diarrhea in less than 24 hours.

Rehydration: Intravenous rehydration is needed only when fluid loss is >10% of body weight (BW). Or if the patient is losing >10 ml/kg/hr or is unable to take oral fluids due to weakness, stupor, vomiting. Volume equivalent to 10% BW should be infused over 2–4 hours, subsequent rate of infusion is matched with rate of fluid loss. Ora Rehydration therapy (ORT) can be instituted after initial volume replacement. If the fluid loss is mild (5–7% BW) or moderate (7.5–10% BW), ORT can be instituted from the very beginning. Patients are encouraged to drink ORS at half to 1-hour intervals. Thirst due to volume depletion provides an adequate driving force. In a weak child refusing to drink ORS, intragastric drip can be used, restoring hydration within 6 hours.

- ORS restores and maintains hydration, electrolyte and pH balance until fluid loss stops, mostly spontaneously. Abundant watery diarrhea with frequent stools can be caused by *Vibrio cholerae*, Enterotoxigenic *E. coli* (ETEC), *Salmonella enteritidis* or by Rota virus which stimulate large volume of fluid secretion by activating CMP in intestinal mucosal cell. ORS remains main therapy.
- Long-term zinc supplementation 20 mg/day for 6–60 months, 10 mg/kg for 0–6 months for 10–14 days following the episode also reduces recurrences of diarrhea over the next 2–3 months.
- Feeding during diarrhea increases intestinal digestive enzymes and cell proliferation in mucosa. Simple foods like breast milk, chicken soup, banana, sago, should be given as soon as the patient can eat.
- **Probiotics:** These are microbial cell preparations, either live or lypophilised powders, help to restore healthy gut flora. Recolonization of gut by lactic acid forming bacteria and yeast restores the balance of gut microflora. Organisms used are—*Lactobacillus* especially *Bifidobacterium*, *Streptococcus*, *Enterococcus faecalis* sp. and the yeast *Saccharomyces boulardii*. Probiotics reduce antibiotic-associated diarrhea.

DRUG THERAPY

1. Targeted antibiotics
2. Probiotics
3. Drugs for inflammatory bowel diseases
4. Non-specific anti diarrheal drugs
   - Invasive diarrhea—slightly loose, smaller volume stools associated frequently with mucus and/or blood. This is associated with abdominal cramps without vomiting. This is due to mucosal invasion by enteroinvasive organisms like *Shigella*, enteropathogenic *E. coli*, *Campylobacter jejuni*, *Salmonella typhimurium*, *Yersinia enterocolitica*, *E. histolytica*, and *Clostridium difficile*.
   - Antimicrobials are needed to treat the underlying bacteria.
   - Traveller's diarrhea typically caused by enterotoxigenic *E. coli*, Campylobacter or virus—Cotrimoxazole 480 mg, BD × 10 days, norfloxacin 400 mg BD, doxycycline 100 mg, BD × 7 days reduce the duration of diarrhea and total fluid needed only in severe cases.

- Rifaximin can also be used for empirical treatment of traveler's diarrhea caused by non-invasive strains of *E. coli* in doses of 200 mg TDS for 3 days. Rifaximin is also used for IBS and for prophylaxis before and after gut surgery.
- Other types of diarrhea like by enteropathogenic *E. coli* (EPEC), *Shigella enteritis, Salmonella, Yersinia enterocolitica* treated by cotrimoxazole, ciprofloxacin 500 mg, BD × 10 days, norfloxacin.
- Cholera—tetracyclines reduce stool volume
- *Campylobacter jujeni*—norfloxacin 400 mg, BD oral for 5 days and other FQs eradicate the organism from the stools and control diarrhea. Erythromycin is useful in children.
- *Clostridium difficile* is associated with antibiotic associated pseudomembranous colitis—DOC—metronidazole/vancomycin oral.

- Diarrhea associated with bacterial growth in blind loops, diverticulitis may be treated with tetracyclines or metronidazole.
- Amoebiasis, giardiasis—metronidazole, diloxanide furoate.

DRUGS FOR INFLAMMATORY BOWEL DISEASE (IBD)

- **Two major types of IBD are**—ulcerative colitis affecting colon and Crohn's disease involving ileum and colon.
- **Sulfasalazine**—the sulfapyridine moiety carries 5-ASA to the colon where it exerts local anti-inflammatory effect. A dose of 3–4 g/day induces remission over a few weeks but relapses are common after stopping the drug.
- **Mesalazine**—the coated formulation with acrylic polymer delivers 5-ASA over the length of jejunum, ileum, colon. It is much better tolerated than sulfasalazine. It is contraindicated in hepatic and renal impairment as it has nephrotoxic potential. A daily dose of 2.4 g.
- **Corticosteroids**—prednisolone 40–60 mg/day is highly effective in controlling symptoms and inducing remission in both UC and Crohn's disease. Symptomatic relief starts within 3–7 days and remission is induced in 2–3 weeks. In more severe disease with extraintestinal manifestations—IV methylprednisolone 40–60 mg IV 12–24 hourly for few days.
- **Immunosuppressants**—used in long-term management of IBD. Because of long latency of response, not suitable for acute flareups but have good remission maintenance and steroid sparing property.
- **Azathioprine**—purine antimetabolite converted to 6 MP, indicated in steroid dependent, steroid resistant, severe flareups. Some patients experience high bone marrow toxicity. Dose—1.5–2.5 mg/kg day.
- **Cyclosporine**—used in severe UC not improving with steroids. IV therapy controls symptoms in 7–10 days, used for 2–3 months till azathioprine takes effect.
- **TNF-α inhibitors**—Infliximab–chimeric anti-TNF antibody used in severe active Crohn's disease not improved with IV steroids and immunosuppressants. Infused IV every 2–8 weeks, produces substantial toxicity—acute reactions, formation of antibodies and lowering of resistance to acquire infection. It is only a reserve drug for refractory disease.

Constipation

Common problem being encountered in modern era due to changed life style and reduced consumption of fibres.

Management starts with getting detailed medical history and assessment of stool type and frequency. Use of Bristol stool chart gives better understanding of constipation.

Pathophysiology: This can be from slow intestinal transit or from poor pelvic floor relaxation during defecation. History and trial of medications will help in differentiating. While slow transit constipation will respond to medications, pelvic floor disorders have poor response. This can be assessed by complex tests like intestinal transit time, defecation proctogram, MRI of pelvis.

Treatment–laxatives: Commonly used to accelerate the movement of food through the GIT tract. These drugs can be classified on the basis of their mechanism of action as irritants, bulking agents and stool softeners. They increase adenylcyclase and c-AMP content of intestinal epithelial cells, resulting in decrease in sodium absorption and stimulation of CL secretion. They cause stimulation of enteric cells and 5-HT containing neuroendocrine cells and initiation of intestinal metabolism of arachidonic acid by cyclo-oxygenase pathway. They are classified into following categories:

- **Stimulant or irritant laxatives:** Irritant oils, e.g. castor oil. Castor oil is obtained from seeds of Ricinus communis. It acts as irritant and produces purgation. The anthraquinones derivatives—cascara sagrada and Senna are present in leaves, pods and roots of these plants. These drugs act on large bowel and produce evacuation after 6–8 hrs, after their ingestion. Others are phenophthalein, bisacodyl, sod. picosulfate.
- **Osmotic laxatives:** Mg sulfate, lactulose, milk of magnesia, magnesium citrate. By osmotic action they hold large volumes of water, increasing the intestinal bulk. Mg $(OH)_2$ and $MgSO_4$ hold water in intestine by osmosis and produce defecation in 1 hour. The dose of $MgSO_4$ is 5–10 g, milk of magnesia 7–8.5%, Mg citrate, sodium pot. Tartarate-8–16 g (Rochelle salt). They are used as iso-osmotic electrolyte solutions containing polyethylene glycol, used as colonic lavage solutions for radiographic or endoscopic procedures. Lactulose is used in the dose of 30–50 ml of the solution with plenty of water 3 times a day in the treatment of hepatic coma.
- **Bulk laxatives:** Natural or semisynthetic polysaccharide and cellulose derivative, when given orally is not absorbed. These agents absorb water and swell up providing stimulus of mechanical distension for evacuation. They act on basis of physical action.
- **Preparations**
  - Agar—the dose is 4 g
  - Ispagol—5–15 g
  - Bran—byproduct of milling of wheat and contain 40% of fibre.

  Methyl-cellulose and carboxymethylcelulose, useful in patients with:
  - Irritable bowel syndrome
  - Hemorrhoids
  - Chronic diarrhea

  The dose is 1 g, 1–4 times daily.
- **Emollient laxatives:** Surface active agents that become emulsified with stool, exert softening and lubricating effect on feces when taken at bed time, e.g. liquid paraffin, Docusate sodium (dicotyl sod. sulfosuccinate). The dose is 100–200 mg TDS. They are

used in constipation due to decreased intestinal tone in food or drug poisoning, following helminthic therapy to eliminate the parasites.

- Laxatives may produce GIT disturbances like dyspepsia, nausea, loss of fluid, and electrolytes, nutritional deficiency, complete dependence on drugs.
- Laxatives are absolutely contraindicated in patients with undiagnosed acute abdomen and in cases with intestinal obstruction.

  Glycerin: Used in the form of rectal suppositories. It acts by osmotic action, softens the stools.

  Enemas: Used for bowel evacuation, used in fecal impaction, to empty the colon and rectum before radiological or endoscopic examination, to cleanse the large bowel prior to surgery, in patients with incontinence or colostomies.

  Prokinetic agents: 5-HT4 receptor agonist, e.g. Tegaserod,

  New drugs *prucalopride, lubipristone*, linaclotide and plecanatide
- Check for hypothyroidism in elderly and hypercalcemia in the young.
- Simple lifestyle changes like increased fibers and use of squatting toilets can work wonders.

Irritable Bowel Syndrome (IBS)

- Irritable bowel syndrome is a condition characterised by any of the symptoms of pain, diarrhea or constipation in the absence of any obvious pathology.
- Treatment depends on the underlying symptoms.
- History may reveal underlying depression or anxiety in many patients.
- Abdominal discomfort with alteration in bowel habits—constipation, diarrhea or both. 5HT3 receptor antagonist, alosetron in IBS with diarrhea 0.5 mg BD for 4 weeks.

EMESIS AND ANTIEMETICS

Introduction

Emesis (vomiting) is the forceful expulsion of gastric or intestinal contents through the mouth. Vomiting is sometimes accompanied by nausea, which is an unpleasant sensation of having the urge to vomit. In the following text, we discuss, in brief, the neurohumoral mechanisms of emesis and, subsequently, antiemetics based on their mechanism of action.

The vomiting centre in the medulla is a functional zone consisting of the reticular formation and nucleus tractus solitarius. This mediates as the conducting zone between vagal afferents reaching the brainstem from peripheral organs via blood vessels and the vagal efferents causing emesis. The chemoreceptor trigger zone (CTZ), which is functionally located outside the blood–brain barrier, is stimulated by various endogenous and exogenous chemicals, stimulating the vomiting centre for emesis. The schematic representation of the viscera, receptors, and central centres for emesis is shown in Fig. 29.3. The receptors involved are the basis of the pharmacotherapy of emesis.

Antiemetics

These are the drugs that prevent or suppress vomiting. They are classified as shown in Fig. 29.4 and their mechanism of action, doses, medication, side-effects are shown in Table 29.1.

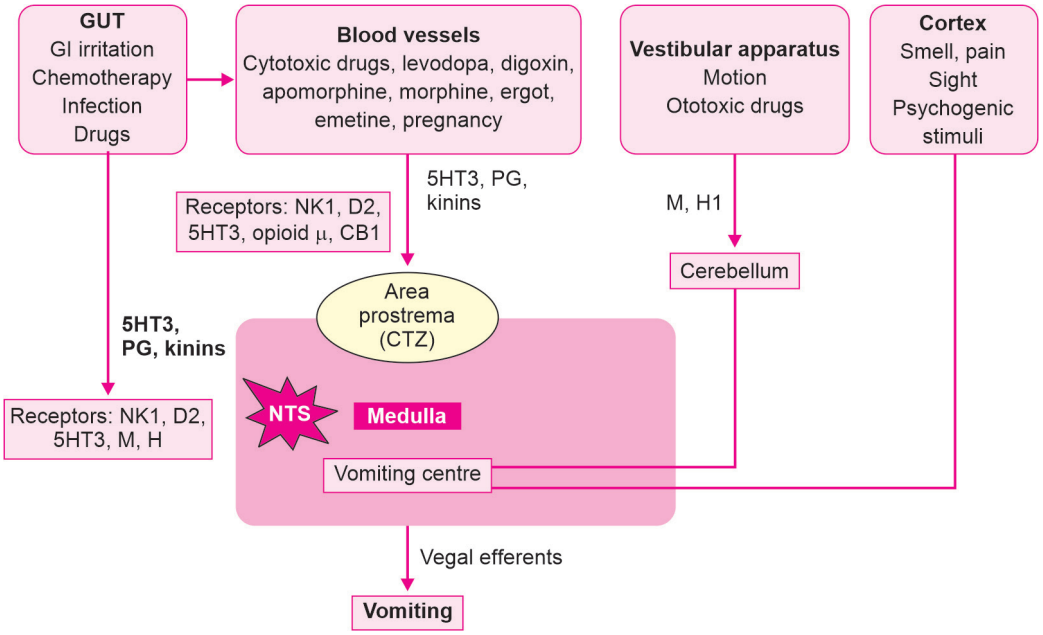

Fig. 29.3: Major central and visceral structures involved in emesis and the neurohumoral receptors mediating the emetic response.

NTS: Nucleus tractus solitarius; CTZ: Chemoreceptor trigger zone; 5HT3: Serotonin; H1: Histamine 1; D2: Dopamine 2; M: Muscarine; NK1: Neurokinin 1; CB1: Cannabinoid 1; GI: Gastrointestinal

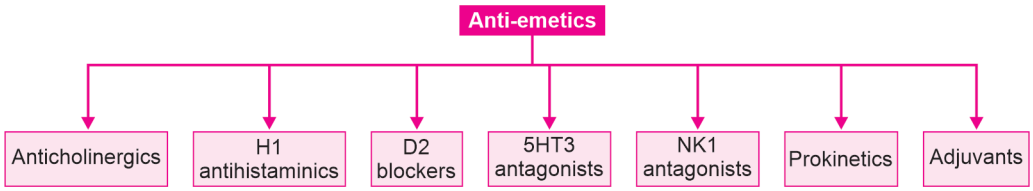

Fig. 29.4: Classification of anti-emetics

Table 29.1: Antiemetics—mechanism of action, doses, indication, side-effects

Class of drugs	*Mechanism of action*	*Examples*	*Indications*	*Side-effects*
Anticholinergics	Anticholinergic drugs can attenuate vestibular inputs to the emetic center, reducing motion-induced nausea and vomiting, also inhibit gastrointestinal motility and vagal inhibition	Hyoscine 0.2–0.4 mg, oral, IM Dicyclomine 20 mg oral/IM	Prophylaxis for motion sickness	Dry mouth, sedation, blurred vision, constipation, urinary retention, and cognitive impairment

Contd.

Table 29.1: Antiemetics—mechanism of action, doses, indication, side-effects

Class of drugs	*Mechanism of action*	*Examples*	*Indications*	*Side-effects*
NK1 antagonists	NK1 receptor antagonists block the action of substance P, a neurotransmitter involved in the emetic reflex	Aprepitant, 125 mg before chemotherapy + 80 mg each on 2nd and 3rd day, oral along with IV ondansetron + dexamethasone Fosaprepitant	Chemotherapy-induced nausea and vomiting (CINV)	Weakness, fatigue, flatulence, and rise in liver enzymes
H1 antihistaminic	Antihistamines block histamine receptors in the vestibular system and CTZ, reducing motion-induced nausea and vomiting. They also possess sedative properties, which can be beneficial for certain conditions	Dimenhydrinate, Diphenhydramine, Meclizine Doxylamine 10–20 mg HS	Motion sickness, vertigo Morning sickness in pregnancy	Sedation, dizziness, dry mouth, blurred vision, urinary retention
D2 blockers	By antagonizing dopamine receptors in the CTZ and possibly other brain regions, these medications suppress the emetic response mediated by dopamine neurotransmission	Metoclopramide, 10 mg, TDS, oral or IM Prochlorperazine oral 5–10 mg, BD Domperidone 10–40 mg, TDS Levosulpiride 25 mg TDS to 75 mg BD	Diabetic gastroparesis, GERD, Chemotherapy-induced nausea and vomiting, migraine-associated nausea and vomiting, and morning sickness.	Drowsiness, fatigue, restlessness, extrapyramidal symptoms (dystonia, tardive dyskinesia)
5HT3 antagonists	These drugs block serotonin receptors in the chemoreceptor trigger zone (CTZ) and gastrointestinal tract, thereby inhibiting the emetic reflex triggered by serotonin release	4.8 mg tab., 2 mg/ml inj. Ondansetron, Granisetron, palonosetron 250 mg by slow IV inj 1/2 hr before chemotherapy	Prevention and treatment of nausea and vomiting associated with chemotherapy, radiation, and postoperative nausea and vomiting (PONV)	Headache, constipation, dizziness, QT interval prolongation

Contd.

Table 29.1: Antiemetics—mechanism of action, doses, indication, side-effects

Class of drugs	*Mechanism of action*	*Examples*	*Indications*	*Side-effects*
Adjuvants Steroids	Corticosteroids have anti-inflammatory properties and can inhibit the release of various cytokines and mediators involved in the emetic response. They are often used as adjunctive therapy for CINV and PONV.	Dexamethasone, 8–20 mg IV before chemotherapy Methylprednisolone	Prevention and treatment of nausea and vomiting associated with chemotherapy	Increased appetite, weight gain, mood changes, insomnia, adrenal suppression on long-term use
Cannabinoids	Cannabinoids exert antiemetic effects through activation of cannabinoid receptors (CB1) in the central nervous system	Dronabinol, Nabilone	Chemotherapy-induced nausea and vomiting (when other treatments have failed).	Sedation, euphoria, dizziness, dry mouth, psychoactive effects
Benzodiazepines	Benzodiazepines have anxiolytic and sedative properties, which can help alleviate anticipatory nausea and vomiting associated with chemotherapy	Lorazepam	Chemotherapy-induced nausea and vomiting	Sedation, dizziness
Antiemetics with unclear mechanism of action		Propofol Pyridoxine (vitamin B_6) Barbiturates Isopropyl alcohol vapour		

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Chapter
30

Treatment of Peptic Ulcer

Peptic ulcer occurs when damaging effects of gastric acid, pepsin outweigh the defence mechanisms' protective effect for the gastric and duodenal mucosa from these substances (Fig. 30.1). Use of non-steroidal anti-inflammatory drugs (NSAIDs) in elderly and *H. pylori* bacterial infection are the major causes of peptic ulcer. Most peptic ulcers can be treated with appropriate medication. The majority of peptic ulcers are caused by *H. pylori*. The most recommended first line treatment is a combination of proton pump inhibitors (PPI) and the antibiotics—amoxycillin and clarithromycin for 2 weeks. In penicillin allergic patients, metronidazole can be substituted for amoxicillin.

Role of Drugs in Peptic Ulcer Disease

- Pain relief
- Healing of ulcer
- To prevent the occurrence of complications
- To prevent relapse.

Pharmacotherapy in Peptic Ulcer

Antacids: Antacids are bases that decrease gastric acidity by neutralizing HCl and pH of gastric contents. Taken empty stomach, a single dose of an antacid acts for short duration only (30–60 minutes). Taken with meals, the action is prolonged to 2–3 hours but the rate of neutralization of HCl will decrease in presence of food in stomach.

Systemic antacids—e.g. sodium bicarbonate. It is absorbed by systemically. It is soluble in water and acts instantaneously but for shorter time.

Adverse Effects

- Produces carbon-di-oxide in stomach causing bloating and discomfort

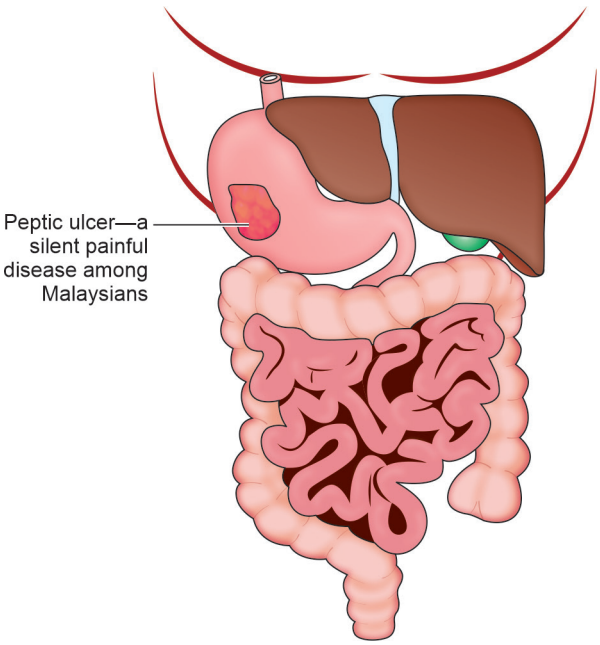

Fig. 30.1: Peptic ulcer

- Acid rebound after cessation of medications
- Increase sodium load, which can worsen anasarca and heart failure.

Non-systemic antacids: Insoluble and polyabsorbed, basic compounds, react in stomach to form corresponding CL salt. The Cl salt reacts with intestinal HCO_3 so that there is no acid base disturbance.

$Mg(OH)_2$ has low water solubility and is efficacious antacid. Magnesium trisilicate is a laxative.

$Al(OH)_3$ binds phosphate in intestine preventing absorption. Hypophosphatemia occurs if used regularly.

Magaldrate: Hydrated complex of hydroxy Mg aluminate. Mg salts are laxative while Al salts are constipating leading to least effect on emptying of gastric contents. Also, the individual component dose is decreased.

$CaCO_3$ is a potent and rapidly-acting neutralizer but causes milk alkali syndrome with milk. Its side effects are: Anorexia, weakness, headache, abdominal discomfort, calcium deposits, renal stones.

Uses: They are generally used to relieve dyspeptic symptoms, e.g. sodium bicarbonate, MgO and hydroxide, $Al(OH)_3$. No single antacid is superior and mixtures are often used. They are no longer needed for healing peptic ulcer as they are not suitable for this purpose.

Used for intercurrent pain relief and acidity. Liquid formulations are preferred, e.g. methyl polysiloxane included in preparations–surface active agents collapse froth, improves dispersion of antacid and GIT reflux.

H2 blockers: They block gastric secretion, cardiac stimulation, uterine relaxation, attenuate fall in BP. They decrease gastric secretion of all phases. Secretory responses to all stimuli are attenuated. 60–70% inhibition of 24-hour acid output is done by usual ulcer healing dose.

Ranitidine: Five times more potent than cimetidine. The side effects are less. The dose is 300 mg at bedtime.

Famotidine is more suitable for Zollinger-Ellison syndrome, for aspiration pneumonia 40 mg OD or 20 mg BD. Roxatidine is twice as potent and longer-acting.

Cimetidine is adequately absorbed orally, crosses placenta and reaches milk. Dose has to be decreased in renal failure. Adverse effects are confusion, headache, restlessness, hallucinations, convulsions, coma in elderly patients. Cimetidine inhibits cyt 450, decreases hepatic blood flow, decreases metabolism of many drugs, e.g. carbamazepine, sulfonylureas, imipramine, lidocaine, nifedipine, quinidine, theophylline, metronidazole, warfarin, phenytoin and phenobarbitone. Antacids decrease absorption of all H2-blockers.

Uses

- **Duodenal ulcer:** Cimetidine 400 mg BD or 800 mg at night causes fast and significant pain relief.
- It requires 8 weeks to cure the gastric ulcer.
- Stress ulcers and gastritis.
- Gastroesophageal reflux disease.

Proton pump inhibitors: Block H^+/K^+ ATPase enzyme which is located in the canaliculi of gastric parietal cells. It totally abolishes acid secretion at rest, stage and also stimulated by food or secretagogues.

- Rabeprazole causes fastest suppression of acid secretion and aids gastric mucin synthesis. Dose is 20 mg OD.
- Lansoprazole: Ulcer healing dose is 15–30 mg OD. Dose should be reduced in liver disease. Pantoprazole is used for IV administration in prophylaxis of acute stress ulcers and bleeding ulcers. Dose is 40 mg OD.
- Esomeprazole is effective in treating gastric/duodenal ulcers and inhibiting *H. pylori.* Dose is 20–40 mg OD.

Uses

1. **Peptic ulcer:** The doses are 20 mg, 40 mg OD for healing gastric ulcers in 4 weeks. Duodenal ulcers heal in 4–8 weeks. IV pantoprazole is drug of choice to control bleeding from peptic ulcer.
2. GI reflux disease.
3. **Zollinger-Ellison syndrome (ZE syndrome):** Pantoprazole 60–120 mg/day IV. Adverse effects: Nausea, loose stools, headache.

   Anticholinergics: Decrease volume of gastric juice without raising its pH, delay emptying, e.g. pirenzepine–selective M1 anticholinergics used in Europe. 50 mg 2–3 times/day for 4–6 weeks.

   Prostaglandin (PG) analogues: PGE2 and PGI2 produced in gastric mucosa protect by inhibiting acid secretion and increasing mucus and HCO_3 secretion.

   – PGs inhibit the production of gastrin, increase blood flow to the mucosa, have marked cytoprotective action.

The natural PGs degrade very rapidly once they have been synthesized, hence have a very short half-life. Stable PG analogues which exert action for hours rather than minutes, have been developed for use in peptic ulcer. Misoprostol has been released in India. The decrease in 24-hour acid production is less than H2-blockers because of shorter duration of action. The dose is 200 µg, daily in 2–4 divided doses. Side effects are diarrhea, abdominal cramps, uterine bleeding. Patient compliance is poor. The drug is contraindicated in pregnancy. Misoprostol is a synthetic PGE1 derivative, used for prevention of NSAIDS-induced ulcers, by the cytoprotective mechanisms.

Ulcer protectives: are drugs that protect the base of a peptic ulcer by increasing mucosal resistance.

Sucralfate by cross-linkage of molecules, polymerises at pH <4 forming a sticky gel like consistency. It precipitates surface protein and acts as a physical barrier preventing acid, pepsin and bile from coming in contact with ulcer. It also increases gastric mucosal PG synthesis. The dose is 1 g 4 hourly daily on an empty stomach.

Colloidal Bi subcitrate is used for healing of benign gastric and duodenal ulcer. It stimulates mucosal PGE_2 production, leading to increased secretion of mucus and HCO_3.

- Collodal Bi subcitrate and mucus form a glycoprotein bi-complex that coats the ulcer and acts as a diffusion barrier to acid in stomach
- Detects *H. pylori* on the surface of mucosa and directly kills this organism.

Adverse effects are diarrhea, headache, and dizziness, and osteoarthopathy, encephalopathy, blackening of tongue, stools, and teeth.

Ulcer healing drugs, e.g. carbenoxolone sodium increases mucus production and increases gastric epithelial cells' lifespan, prevents reflux of bile, causes slowing of PG degradation—Na and water retention and K^+ loss. Dose—20 mg TDS oral.

DRUGS FOR *HELICOBACTER PYLORI* INFECTION

H. Pylori is a Gram-negative bacillus that attaches to surface epithelium under the mucus. It posssess high urease activity. It maintains a neutral microenvironment around the bacteria by producing ammonia and causes H^+ ions back diffusion. *H. Pylori* infection once established can last for the life of the host.

Antimicrobials found clinically effective against *H. Pylori* are amoxycillin, clarithromycin, metronidazole. Resistance develops rapidly to metronidazole.

The one or two-week regimens are used using 2 or 3 drugs.

One-week regimens not recommended now due to high failure rates.

Two-week regimens

- Amoxycillin 500 mg TDS + Clarithromycin 250 mg TDS + Omeprazole 20 mg BD.
- Amoxycillin 1000 mg BD (or metronidazole 400 mg TDS) + Clarithromycin 500 BD + Omeprazole 30 mg BD.

Long term acid suppression therapy is needed only in *H. pylori* negative cases or those in whom this organism can not be eradicated.

Vonoprazan: Acts by inhibiting the proton pump of the gastric parietal cell by binding of K^+ ions to hydrogen/potassium adenosine triphosphate (H^+/K^+ ATPase) enzyme system. It is a potassium-competitive acid blocker (PCAB). It increases gastric pH and inhibit gastric acid production, dose is 20 mg once daily oral for 8 weeks for gastric ulcer and 6 weeks for duodenal ulcer.

Patients not responding in their symptoms to one PPI can benefit if the PPI is changed to another. Vonoprazan is now increasingly used for treatment of *H. pylori* due to increased efficacy.

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Chapter
31

Treatment of Liver, Intestine, and Pancreatic Diseases

JAUNDICE

Defined as yellow discoloration of sclera due to increased bilirubin level in blood. This occurs due to high bilirubin not being excreted by liver

Causes can be prehepatic, hepatic or post hepatic.

Prehepatic occurs in condition like hemolysis, rhabdomyolysis where the production of bilirubin is more than what can be excreted from liver.

Post-hepatic hyperbilirubinemia (obstructive jaundice) occurs when flow of bilirubin is obstructed in bile ducts, e.g. stone in common bile duct.

Hepatic hyperbilirubinemia occurs when bilirubin excretion is impaired due to liver dysfunction, e.g. viral hepatitis, drugs.

Clinical features: Hepatomegaly with a smooth tender liver is seen in hepatitis and with extrahepatic obstruction, but a knobby irregular liver suggests metastasis. Splenomegaly indicates portal hypertension in patients when signs of chronic liver disease are present. Ascites is found in cirrhosis but can also be due to carcinoma.

Investigations: Viral markers for HAV, HAV B and HCV and USG. The liver biochemistry confirms the jaundice and may help in the diagnosis. In hepatitis, serum aspartate aminotransferase (AST) and alanine transaminase (ALT) tend to be high early in the disease. Conversely, in extrahepatic obstruction the alkaline phosphatase (ALP) is high with a smaller rise in aminotransferases. USG will demonstrate the size of bile ducts, which are dilated in extrahepatic obstruction and the level of obstruction and the cause of the obstruction.

Management: Treatment of underlying condition.

Hepatitis is defined as inflammation of liver.

Seen in clinical practice as increase in liver enzymes, clinically patient may have loss of appetite, nausea, vomiting, fever and abdominal discomfort.

This can be from damage to liver called hepatotoxic hepatitis or from predominant damage to bile ducts called cholestatic hepatitis.

Hepatotoxic hepatitis is caused by virus, drugs, infections and alcohol. Common viruses which affect the liver are hepatitis A, B, C and E Hepatitis A and hepatitis E are transmitted by feco–oral route. Management of hepatitis A and E is usually supportive.

Most patients recover spontaneously while patients with hepatitis E in immunocompromised state may have prolonged course.

Ribavirin has been used for hepatitis E in immunocompromised patients. Dose of 600–800 mg per day for 12 weeks. It acts by epigenetic changes in virus and reduces virus load.

Side-effects: Hemolysis is important side-effect with use of ribavirin, hence monitoring of hemoglobin is required while on treatment with riabvirin.

Hepatitis B and hepatitis C are transmitted through parenetral route or sexual transmission. Acute hepatitis B resolves spontaneously in most adults however treatment may be required in cases of acute hepatitis when there is decompensation of liver.

Hepatitis C needs treatment if HCV-RNA persists for more than 12 weeks when acute or when chronic hepatitis is present. Treated with direct acting antivirals which is combination of drugs—ledipasvir and sofosbuvir, elbasvir and grazoprevir.

Uncomplicated hepatitis C is treated with sofosbuvir 400 mg + Daclatasvir 60 mg × 84 days. CBC, LFT and S. creatinine are monitored. Early diagnosis and treatment can prevent severe complications such as cirrhosis and liver cancer.

Drugs used in treatment of hepatitis B

- **Nucleoside/nucleotide analogues:**
  - Lamivudine
  - Adefovir
  - Entecavir
  - Tenofovir disoproxil fumarate
  - Tenofovir alafenamide
- Hepatitis B and C cause worldwide morbidity and mortality.

Lamivudine: Its half-life ($t_{1/2}$) is short but intracellular $t_{1/2}$ is 12–18 hrs and more prolonged in HBV than HIV and used 100 mg OD. Lamividine inhibits replication of HBV by inhibiting transcription of intermediate RNA. It can safely be used in decompensated liver disease. Development of resistance after 8–9 months is the limitation.

Adefovir dipivoxil: It is adenosine analogue developed for treatment of HIV but also effective for HBV infection in doses lower than HIV. It is converted to active diphosphate metabolite by cellular kinases and this is incorporated in viral DNA and causes chain termination by inhibiting HBV-DNA polymerase. Oral BA is increased with ibuprofen and not affected by food. It is active against lamivudine resistant strains of HBV and resistance to adefovir does not develop even after treatment for one year.

Tenofovir: 300 mg OD for 48 weeks, has good efficacy, low resistance, and safety. It is DOC for HBV infection including cases resistant to lamivudine. It is also used for HIV-AIDs.

Ribavirin: It is guanosine analogue and converted into active phosphorylated form by intracellular enzyme of host cell. It inhibits the synthesis of guanosine triphosphate and inhibits viral mRNA and viral RNA dependent RNA polymerase. It has broad spectrum antiviral action and is active against both RNA and DNA viruses and includes influenza virus A and B, RSV, paramyxovirus, HCV and HIV 1. It is used orally mainly for hepatitis C alone and in combination, more effective with interferon for 24–28 weeks is considered standard and first-line treatment for hepatitis C. It can be used orally or IV (in severe cases) for influenza and for RSV infections as aerosol through nebulizer in children.

Hepatitis is a vaccine preventable disease. All healthcare workers should be vaccinated for hepatitis B. 3 doses at 0, 1 and 6 months.

Chronic Liver Disease

As suggested by name itself, this is a condition in which liver is affected for a long duration of time and leads to cirrhosis of liver.

Cirrhosis causes hardening and irregular contour of liver and resultant portal hypertension (Fig. 31.1). As a consequence, complications occur like ascites, esophageal and/or gastric varices, encephalopathy, liver cancer.

Treatment is needed for complications and early identification of complications is essential

Ascites occurs due to hyper-aldosteronism and causes fluid accumulation in peritoneum. Management for ascites is drug and diet.

Reduce total salt intake to less than 2 g of sodium chloride per day.

Paracentesis is used to relieve symptomatic tense ascites or when diuretic therapy does not control accumulation of fluid. The main complication is hypovolemia and renal dysfunction.

Spironolactone can be started if fluid overload is non-responsive, starting from 25 mg per day to maximum of 400 mg per day as tolerated. Furosemide can be added to maximum dose of 160 mg per day.

However, in patients with renal impairment, serum potassium can go up and creatinine can worsen even with smaller dose, hence regular monitoring of renal function is needed.

Spontaneous bacterial peritonitis occurs because of infection of the ascitic fluid usually by Gram-negative bacteria manifesting as abdominal pain and fever.

Diagnosis is established by diagnostic ascitic tap which shows high neutrophil count of more than 250 cells/µl or culture shows presence of bacteria.

It is treated by ciprofloxacin or IV ceftriaxone.

Primary prophylaxis with norfloxacin can be given to patient with advanced liver cirrhosis or when protein content is less than 10 g/L in ascitic fluid.

Hepatocellular carcinoma (HCC) develops in patients with liver cirrhosis at rate of 1–3% per annum, regular surveillance for HCC is needed in patients with liver cirrhosis to detect HCC at early stage.

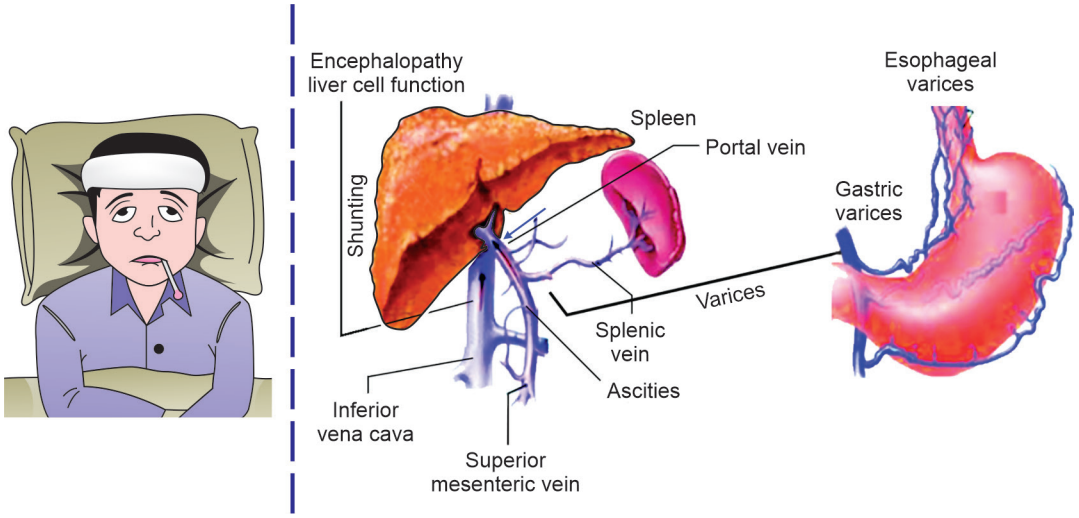

Fig. 31.1: Portal hypertension

Variceal bleeding occurs due to increased pressure of the portal system causing blood vessels to rupture.

Treatment is endoscopic intervention by either banding or direct injection of the varices with histacryl. Somatostatin is used to reduce portal pressure in dose of 250 μg/hour given for 3–5 days. Terlipressin can be used as alternative, 2 mg 6 hourly, reducing to 1 mg 4 hourly after 48 hours.

Hepatic encephalopathy occurs due to effect of toxins in brain causing altered sleep cycle, lack of concentration to drowsiness and coma.

Give purgation and enemas to empty the bowels of nitrogenous substances.

Treatment is by use of lactulose 10–30 ml TDS, which is an osmotic purgative, reduces colon pH and limits ammonia absorption to increase bowel opening.

Treatment of precipitating factor: Rifaximin which is nonabsorbable antibiotic can be used if encephalopathy is recurrent.

Inflammatory bowel disease (IBD)—is comprised of two major disorders: Ulcerative colitis and Crohn's disease. Ulcerative colitis affects the colon, whereas Crohn's disease can involve any component of the gastrointestinal tract from the mouth to the perianal area.

Ulcerative colitis: Chronic inflammation which has relapsing and remitting episodes of inflammation limited to the mucosal layer of the colon. Always involves the rectum, and often involves other parts of the colon in a continuous fashion.

Crohn's disease—has transmural inflammation with skip areas of involvement in which there are patches of normal appearing bowel interrupted by areas of Crohn's disease. The transmural inflammatory nature of Crohn's disease may lead to fibrosis and strictures and to obstructive clinical presentations that are not typically seen in patients with ulcerative colitis. Transmural inflammation may also result in sinus tracts, giving rise to microperforations and fistula formation.

Treatment depends on the severity of disease and areas of involvement.

Medications for ulcerative colitis (UC):

- Antibiotics
- For mild-to-moderate UC—treated with 5-ASA oral and with topical ASA
- Use steroids if non-responsive—prednisolone, budenoside

Crohn's disease treatment depends on type, treatment is complex and involves combination of 5-ASA and biologics.

Biologics—four anti-TNF agents (infliximab, adalimumab, golimumab and certolizumab pegol) and two anti-integrin agents (natalizumab and vedolizumab) are used for Crohn's disease.

Pancreatitis—inflammation of pancreas

Confirmed by presence of a least 2 of the 3 criteria

1. Typical pain—central pain in epigastrium which radiates to back
2. Amylase more than 2 times upper limit of normal.
3. Imaging features suggesting pancreatic necrosis seen on CT scan or ultrasound abdomen or MRI.

Causes: Stone in ampulla of common bile duct and pancreas confluence, alcohol, virus, drugs.

Treatment: Identify the underlying cause and precipitating factors to be removed.

IV hydration is crucial at early stage.

A daily lipase intake of up to 10,000 units/kg body weight is required.

Antibiotics needed only if infection is confirmed, not recommended to start prophylactic antibiotics.

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Chapter
32

Treatment of Diabetes Mellitus

- It is a metabolic disorder characterized by hyperglycemia, glycosuria, hyperlipidemia, negative N_2 balance and ketonemia.
- Accumulation of large quantities of sorbitol in tissues is to be causative in pathological change of diabetes. The concentration of glycosylated Hb (HbA1c) is taken as an index of protein glycosylation. It reflects the state of glycemia over the preceding 2–3 months. There are 2 major types of diabetes mellitus (DM).
- **Type 1** diabetes mellitus—insulin dependent DM (IDDM). It is an autoimmune disorder in juvenile population <30 years. Antibodies that destroy β-cells are detected in blood. Insulin in circulation is low or absent and patients are more prone to ketosis. It is a slow autoimmune disease with HLA linked genetic predisposition.
- **Type 2** diabetes mellitus—non-insulin dependent DM (NIDDM) in >40 years population. Insulin in circulation is normal or even high. No anti β-cell antibodies are demonstrable. There is high genetic predisposition onset past middle age. It is due to abnormality in β-cells so that they respond at high glucose concentration and there is excess of hyperglycemic hormones.

SECONDARY TO OTHER PATHOLOGY

1. Pancreatitis, hemochromatosis, neoplastic disease, cystic fibrosis and pancreatectomy.
2. Excess endogenous secretion of hormonal antagonists to insulin: Growth hormone, glucocorticoids, thyroid hormones, catecholamines, human placental lactogen, glucagon, counter-regulatory hormones, severe burns, trauma.
3. Medication with corticosteroids, thiazide diuretics, phenytoin.
4. Obesity
5. Associated with genetic syndromes.
   a. **Didmoad:** Diabetes insipidus, diabetes mellitus, optic atrophy, nerve deafness.
   b. Muscle dystrophy
   c. Down's syndrome
   d. Turner's syndrome
   e. Klinefelter's syndrome.

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin. Lack of insulin leads to reduced carbohydrate metabolism; increased metabolism of proteins and lipids. Death may result from acute metabolic

decompensation while long standing metabolic derangement is associated with permanent and irreversible functional and structural changes in the cells of the body, those of the vascular system being particularly susceptible. These changes lead to complications of diabetes which most characteristically affect the eye, the kidney and the nervous system.

Long-term Complications of Diabetes

- Chronic complications include microvascular complications (retinopathy, nephropathy, neuropathy) and macrovascular complications (hypertension, coronary artery disease, peripheral vascular disease, cerebrovascular disease).
- **Diabetic retinopathy** includes microaneurysms and hemorrhages in retina with exudates, neovascularization, vitreous hemorrhage, and fibrosis.
- **Diabetic nephropathy** is major cause of premature death from end-stage renal disease and cardiovascular disease.
- **The diabetic neuropathy** can be:
  a. Sensorimotor neuropathy—(1) acute—hyperaesthesia, paresthesia, feeling of numbness (2) Chronic—takes years and nerve function unlikely to improve.
  Treatment—tricyclic antidepressants, e.g. amitriptyline 25–50 mg at night time HS.
  b. Mononeuropathy—including carpel tunnel syndrome, cranial nerves 3rd and 6th involved.
  c. Autonomic neuropathy.
- **Metabolic complications**—diabetic ketoacidosis, hyperosmolar hyperglycemic coma

Clinical Features of Autonomic Neuropathy

- **CVS**—postural hypotension, resting tachycardia, sudden cardiorespiratory arrest
- **GIT**—diarrhoea, esophageal dysfunction, fecal incontinence, gastroparesis, constipation
- **Genitourinary**—erectile dysfunction, neurogenic bladder, retrograde ejaculation, cystopathy
- **Sudomotor**—gustatory sweating, nocturnal sweats, anhidrosis–fissures in feet.
- **Vasomotor**—feet constantly cold due to loss of skin vasomotor responses.
- Dependent edema due to loss of vasomotor tone and increased vascular permeability.

The diabetic nephropathy presents as diffuse glomerulosclerosis, nodular glomerulosclerosis: uremia and microalbuminuria.

Clinical Features: Type 1 and 2 Diabetes Mellitus

- Feeling more thirsty than usual
- Frequency of urination increased
- Ketonuria
- Feeling tired and weak or irritable
- Blurred vision
- Slow healing sores
- Prone to infections of gum, skin and vagina

OTHER CATEGORIES

- Potential or prediabetics are persons with a normal glucose tolerance test who have an increased risk of developing diabetes for genetic reasons, i.e. an individual who has a first degree relative with diabetes.

- **Latent diabetics** are persons in whom the glucose tolerance test (GTT) is normal but who are known to have an abnormal result under conditions imposing a burden on the islet β cells, e.g. during pregnancy, infection or severe stress, mental or physical, during treatment with corticosteroids, thiazide diuretics or other diabetogenic drugs or when overweight.
- **Clinical features of potential and latent diabetes:** They complain of no symptoms and show no abnormality on examination. They are predisposed to coronary and peripheral arterial disease, and have increased incidence of stillborn, abnormally large and heavy babies with congenital defects.
- **Gestational diabetes:** Hyperglycemia occurs for the first-time during pregnancy in individuals who are genetically susceptible to develop diabetes. Even minimum hyperglycemia in pregnancy is associated with increased perinatal mortality and morbidity, making it essential to detect and treat these cases effectively. Glycosuria is common in normal pregnancy due to fall in renal threshold for glucose secondary to increase in GFR and in late pregnancy lactose appears in urine. The findings of reducing substances in urine of a pregnant woman should never be dismissed and in all cases, the blood glucose concentration should be carefully measured.

Diagnosis of Diabetics

If the patient complains of symptoms suggesting diabetes.

- Test urine for glucose and ketones
- Measure random blood sugar (RBS), plasma electrolytes, HbA1c >6.5.

Indications for Glucose Tolerance Test (GTT)

- Glycosuria + ketonuria found on routine urine test
- Patient has minimal or no symptoms
- RBS >200 mg/dl

Glucose tolerance test: The patient should have been taking an unrestricted carbohydrate diet for at least 3 days prior to the test, fasts overnight. A sample of blood is taken to measure the fasting blood glucose level and 75 g glucose dissolved in 300 ml of water is given orally. Thereafter samples of blood are collected at half hour intervals for at least 2 hours and their glucose content is estimated.

INSULIN

- Insulin is a simple protein consisting of 51 aminoacids arranged as two polypeptide chains connected by disulfide bonds (Fig. 32.1). Altering aminoacids within the molecule gives new derivatives with differing pharmacokinetics and binding affinity for insulin receptor. Insulin is continuously secreted at a low basal level during fasting. A postmeal rise in serum glucose or aminoacids raises blood levels of insulin severalfold. Other nutrients like arginine, leucine, hormones e.g. glucagon, cholecystokinin, pancreozymin, adrenocorticotropin, modulate insulin release. Insulin secretion is augumented by vagal stimulation and diminished by sympathetic stimulation. The secretion of insulin from α-cells is regulated by chemical, hormonal and neural mechanisms (Fig. 32.2).
- **Actions of insulin**—has profound effects on glucose, fat, protein and electrolytes.
- Facilitates glucose transport across cell membrane by ATP-dependent translocation via glucose transporters—GLUT4 and GLUT1 to plasma membrane and also increasing their activity.

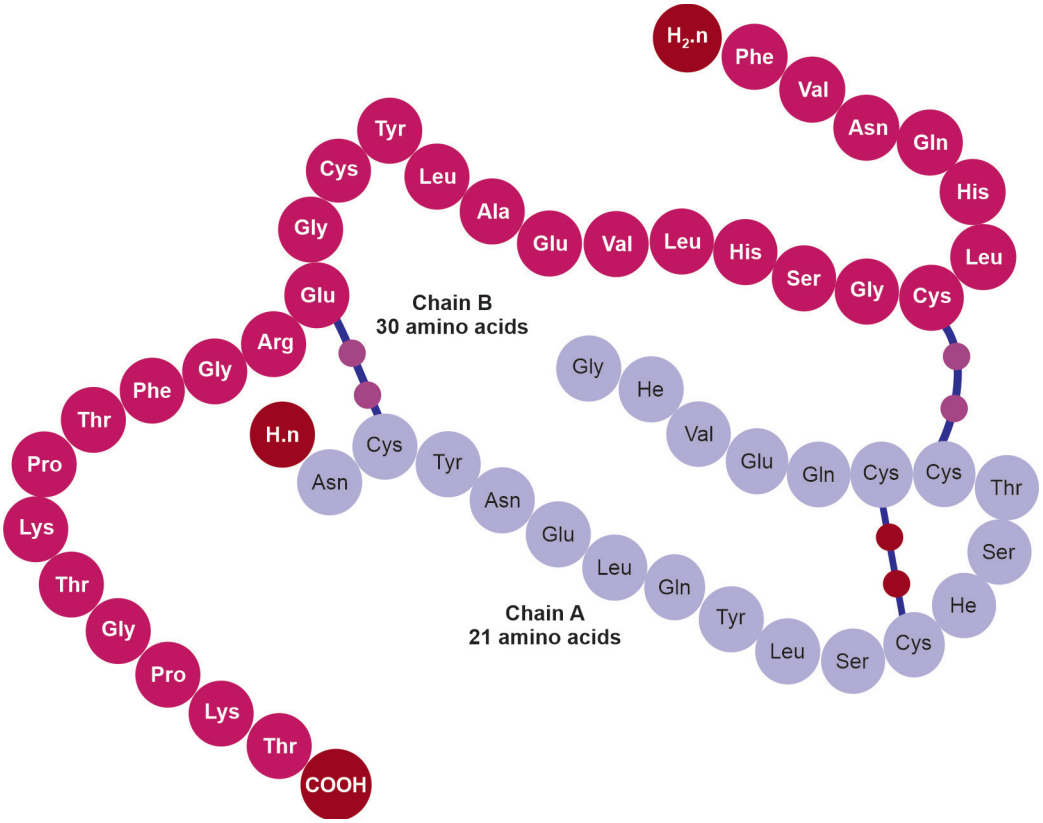

Fig. 32.1: Human insulin structure

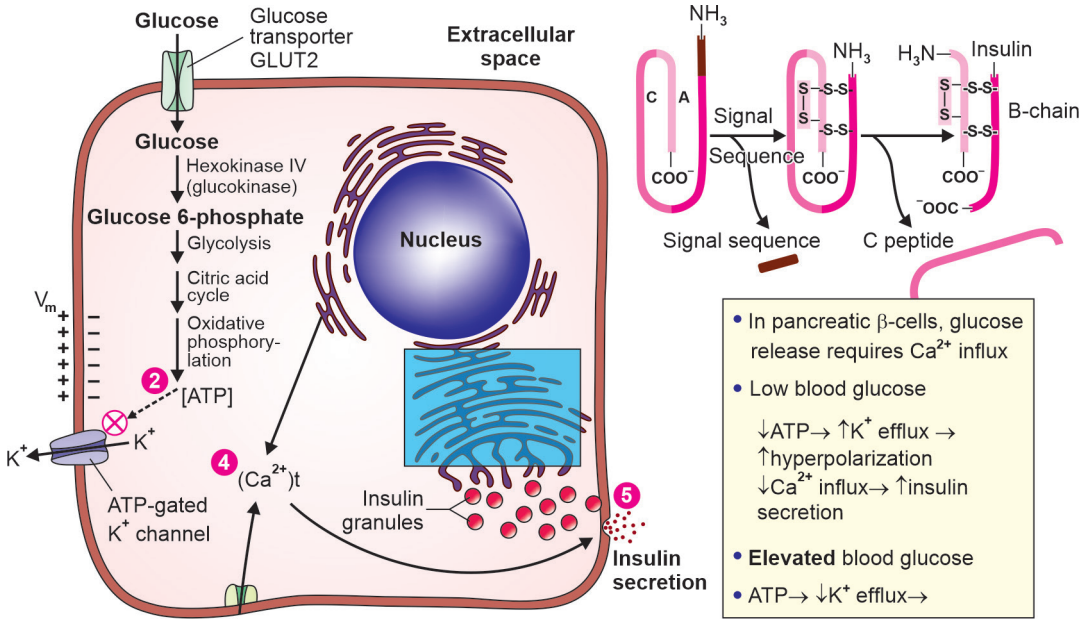

Fig. 32.2: Glucose-mediated insulin release

- Facilitates glycogen synthesis.
- Inhibits gluconeogenesis in liver.
- inhibits lipolysis in adipose tissue and favour triglyceride synthesis.
- Stimulates vascular endothelial lipoprotein lipase and increases clearance of VLDL and chylomicrons.
- Facilitates aminoacid entry and their synthesis into proteins. The above metabolic actions of insulin exerted within seconds or minutes are called rapid actions.

Insulins: The older preparations of insulin contain 1% (10,000 ppm) or other proteins which are potentially antigenic. More purified insulin preparations are obtained according to purification method by gel filtration and repeated crystalline methods.

- **Single peak insulins**—actrapid (50–200 ppm), monotard.
- **Monocomponent insulins**—after insulin is purified by ion exchange chromatography

TYPES

Short-acting

Regular insulin (soluble): Its effect appears in 30 min and peaks between 2 and 3 hrs. after subcutaneous injection.

PIZ suspension (prompt insulin) Zn suspension or semilente.

Intermediate-acting

- Insulin Zn suspension (IZS) or LENTE
- Neutral protamine hagedorn (NPH) or Isophane insulin—has onset of action in 1—2 hours.

Long-acting Insulins have Onset of Action in 2–4 hrs.

- Extended IZS (ultralente).
- Protamine Zn insulin (PZI).

Human insulins: In the 1980s, were produced by recombinant DNA technologies in *E. coli* and yeast. These preparations are expensive with greater stability, less allergic reactions, less insulin resistance, less lipodystrophy. Human insulins and analogs are commonly used, except for considerations of cost. Human insulin is more water soluble and hydrophobic than porcine or bovine insulin. It has slightly more rapid, earlier and more defined peak and slightly shorter duration of action.

Insulin analogs: Using recombinant DNA technology, analogs of insulin have been prepared with modified pharmacokinetics on SC inj. but similar pharmacodynamics. This modification results in more rapid absorption, a quicker onset and a shorter duration of action after SC injection. Greater stability and consistency are other advantages. Modification of amino acid sequence of regular insulin produces analogs that are rapid acting insulins which exert their effects 5–10 minutes after administration.

- Insulin lispro can be injected at the time of meal. A better control of mealtime glycemia and a lower incidence of late post prandial hypoglycemia have been obtained. Using a 2–3 daily insulin lispro as mealtime injections causes a greater HbA1c reduction compared to regular insulin.
- Insulin aspart and glulisine is rapid acting insulin analogue.

- Insulin glargine is suitable for once daily injection to provide background insulin action. Disadvantages it does not control meal time glycemia for which rapid acting insulin or an oral hypoglycemic is used concurrently.
- Insulin detemir and degludec–long-acting insulins.
- Because of acidic pH, glargine cannot be mixed with any other insulin preparations, must be injected separately.

The duration of action of rapid-acting insulins is 3–5 hours, of short-acting insulins is 6–8 hours, of intermediate acting is 20–24 hours and of long-acting insulins is 24 hours.

Insulin is injected subcutaneously in the abdomen/buttocks/anterior thigh/dorsal arm, before each meal.

REACTIONS TO INSULIN

Hypoglycemia—sweating, anxiety, palpitation, tremor due to sympathetic stimulation, those due to glucose deficiency to the brain–dizziness, headache, visual disturbance, hunger, fatigue, weakness.

Treatment: Glucose given orally/IM reverses symptoms rapidly.

- Lipodystrophy
- Allergy
- Edema
- Hypokalemia
- Weight gain

Uses of insulin: Insulin is effective in all forms of diabetes mellitus and must for Type 1 DM. Type 2 DM cases could be first controlled by diet, decrease in body weight and appropriate exercise.

Insulin is needed only in Type 2 DM when:

- Not controlled by diet and exercise
- Failure of oral hypoglycemics
- Underweight patients
- Temporary therapy to tide over infection, trauma, surgery, pregnancy.
- Any diabetic complications—diabetic ketoacidosis, hyperosmolar hyperglycemic coma

Treatment of diabetic ketoacidosis: A minority of cases of type 1 diabetes first present as severe ketoacidosis, precipitated by infection, trauma, surgery, illness. In such cases, patient may present with abdominal pain and vomiting. In the fulminating case, salt and water deficit occurs causing loose dry skin, a furred tongue and cracked lips, tachycardia, hypotension and reduced intraocular pressure. Kussmaul breathing or air hunger is present which is deep and rapid due to acidosis, breath is usually fetid and the sticky sweet smell of acetone may be apparent. Patient may present with mental apathy, confusion or coma.

Treatment: The dose of regular insulin is bolus 0.1–0.2 U/kg IV followed by 0.1–0.2 U/kg/hr IV infusion. NS @1L/hr. Followed within 4–6 hours, blood glucose reaches 300 mg/dl. Change IV fluids to ½ NS with 5% glucose added. Maintain till patient becomes fully conscious. The dose of routine therapy is done with subcutaneous insulin therapy.

- IV fluids are vital to correct dehydration:
- KCl—10–20 meq/hr
- $NaHCO_3$—50 mEq to IV fluids

- Phosphates—5–10 mmol/hour infusion
- Antibiotics

Hyperosmolar hyperglycemia coma: In elderly, type 2 DM causes glucose accumulation > 800 mg/dl. Blood osmolarity >350 milliosm. leading to coma and death. Treatment is the same except faster fluid replacement is instituted and alkali is given. The patient is prone to thrombosis.

Insulin resistance: Insulin resistance is there when required >200U/day and physiologically >100U/day.

Acute resistance develops rapidly, causes are infection, trauma, surgery, emotional stress. Remove the precipitating cause and give higher doses of regular insulin.

Chronic reistance is seen in patients for years with conventional preparations of beef or pork insulins. There are antibodies to homologus contaminating proteins. Development of insulin resistance is an indication for switching to pure preparations.

INDICATIONS FOR PURE INSULINS

- Hypoglycemia
- Insulin resistance
- Allergy
- Injection site lipodystrophy

The short-acting insulins during 3 meal times are given by dosing according to sliding scale (Table 32.1).

Table 32.1: Novalog sliding scale for rapid/short-acting insulin

Blood glucose mg/dl	*Highly insulin sensitivity*	*Normal insulin sensitivity*	*Highly insulin resistant*
<150	0U	0U	0U
150–199	1U	2U	3U
200–249	2U	4U	6U
250–299	3U	6U	9U
300–349	4U	8U	12U
≥350	5U	10U	15U

Oral hypoglycemics: Lower blood glucose levels and are effective orally. Oral hypoglycemics are indicated only when not controlled by diet and exercise. The indications are:

- Duration of disease <5 years when starting treatment
- Age >40
- Obesity
- Fasting blood sugar <200 mg/dl
- Insulin requirement <40 U/day
- No ketoacidosis or other complications
- **Sulfonylureas**—cause direct stimulation of insulin release from the pancreatic β-cells. The sulfonylurea receptor is ATP sensitive potassium channel present on β-cell membrane.

Closure of these channels causes β cell membrane depolarization triggering opening of calcium channels–calcium influx causes degranulation to cause insulin release. They sensitise the target tissues to the action of insulin. All are well absorbed orally. Cautiously used in patients with liver or kidney dysfunction.

- **Tolbutamide**—is short-acting drug, useful in patients prone to hypoglycemia, 0.5–3 g.
- **Gliclazide**—40–80 mg. It has extrapancreatic action, antiplatelet action, delays retinopathy and reduces free radical formation.
- **Glyburide**—2.5 mg/day. It is contraindicated in hepatic and renal insufficiency.
- **Glypizide**—2.5 mg upto 40 mg. It is contraindicated in patients with hepatic and renal impairment.
- **Glimepiride**—used as monotherapy or in combination with insulin, 1 mg up to 6–8 mg

In young patients, glibenclamide is chosen. In elderly, tolbutamide is potent, faster and short-acting.

Adverse effects are hypoglycemia, nausea, vomiting, hypersensitivity, rashes, photosensitivity. Chlorpropamide causes cholestatic jaundice, dilutional hyponatremias, alcohol intolerance.

Biguanides suppress hepatic gluconeogenesis, enhances binding of insulin to its receptor, promotes peripheral glucose utilization, inhibits intestinal absorption of glucose. Adverse effects—most common with phenformin–lactic acidosis. Vitamin B_{12} deficiency is due to metformin. Biguanides are contraindicated in hypotensive states, cardiovascular (CVS), Respiratory, hepatic, renal disease and alcoholics. The dose of metformin is 500–1000 mg OD or BD depending on blood sugar levels. Metformin promotes weight loss and prevents macrovascular and microvascular complications of diabetes.

Alpha Glucosidase Inhibitors

They slow the rate at which carbohydrates are absorbed from the gastrointestinal tract.

Acarbose—oligosaccharide inhibits glucosidase in brush border of small intestinal mucosa, decrease absorption of polysaccharide, mild hypoglycemic. Dose—50–100 mg TDS.

Miglitol—it is also absorbed systemically, inhibits sucrase and maltase also. It does not undergo metabolism and is excreted through renal route. Dose—25–100 mg TDS.

Voglibose—Dose—200–300 μg TDS.

Meglitinides

These are insulin secretagogues. Repaglinide maximum—0.5 mg nateglinide—60–120 mg

They stimulate very rapid and transient release of insulin from β-cells through closure of ATP sensitive K^+ channel. They binds to different binding site on sulfonylureas receptor–closure of ATP-dependent K^+ Channels—depolarisation—insulin release.

Decrease in postprandial hyperglycemic (PPHG) meal adjusted dose gives greater flexibility for busy patients. Repaglinide is avoided in liver disease.

Thiazolidinediones (TZDs)—Selective agonists of nuclear PPARγ—nuclear peroxisome proliferator activated receptor. It increases transcription of insulin responsive genes and reverse insulin resistance by stimulating GLUT4 expression and translocation. TDZs commonly cause edema that can be quite severe. They benefit patients with substantial insulin resistance or requiring insulin >100 U day. Pioglitazone is taken OD in the dose of 15–30 mg and rosiglitazone in the dose of 4–8 mg.

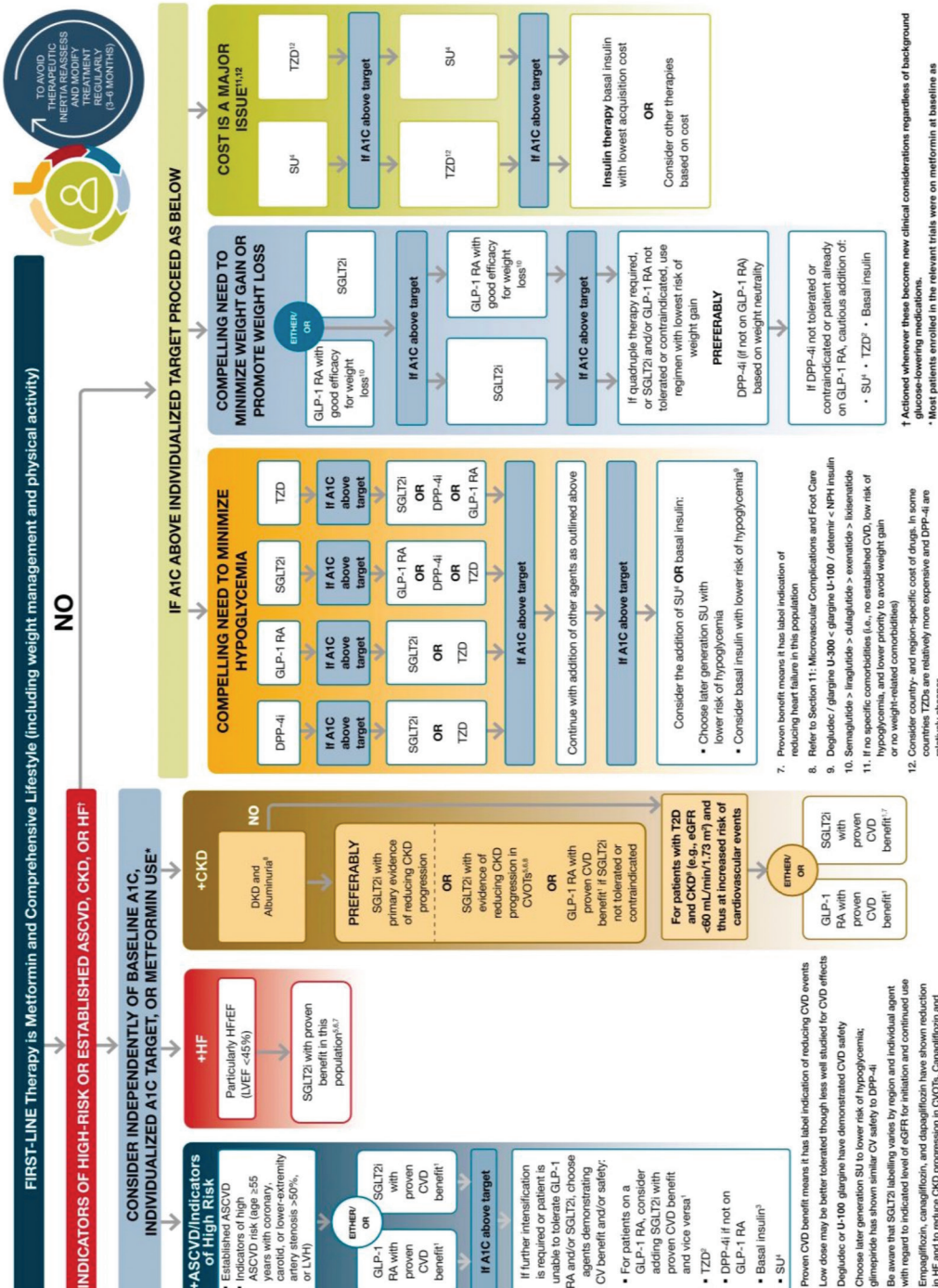
FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)
NO
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF[1]
CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*
+ASCVD/Indicators of High Risk
• Established ASCVD
• Indicators of high ASCVD risk (age ≥55 years with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1]
If A1C above target
If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety:
• For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa[1]
• TZD[2]
• DPP-4i if not on GLP-1 RA
• Basal insulin[3]
• SU[4]
+HF
Particularly HFrEF (LVEF <45%)
SGLT2i with proven benefit in this population[4,6,7]
+CKD
DKD and Albuminuria[4]
NO
PREFERABLY
SGLT2i with primary evidence of reducing CKD progression
OR
SGLT2i with evidence of reducing CKD progression in CVOTs[4,8]
OR
GLP-1 RA with proven CVD benefit[1] if SGLT2i not tolerated or contraindicated
For patients with T2D and CKD[5] (e.g., eGFR <60 mL/min/1.73 m²) and thus at increased risk of cardiovascular events
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1,7]
IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW
COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
If A1C above target
GLP-1 RA
If A1C above target
SGLT2i
If A1C above target
TZD
If A1C above target
SGLT2i OR TZD
If A1C above target
SGLT2i OR TZD
If A1C above target
GLP-1 RA OR DPP-4i OR TZD
If A1C above target
SGLT2i OR DPP-4i OR GLP-1 RA
If A1C above target
If A1C above target
Continue with addition of other agents as outlined above
If A1C above target
If A1C above target
Consider the addition of SU[4] OR basal insulin:
• Choose later generation SU with lower risk of hypoglycemia
• Consider basal insulin with lower risk of hypoglycemia[9]
If A1C above target
COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
EITHER/ OR
GLP-1 RA with good efficacy for weight loss[10]
SGLT2i
If A1C above target
SGLT2i
GLP-1 RA with good efficacy for weight loss[10]
If A1C above target
If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain
PREFERABLY
DPP-4i (if not on GLP-1 RA) based on weight neutrality
If A1C above target
If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
• SU[4] • TZD[2] • Basal insulin
COST IS A MAJOR ISSUE[11,12]
SU[4]
TZD[12]
If A1C above target
TZD[12]
SU[4]
If A1C above target
Insulin therapy basal insulin with lowest acquisition cost
OR
Consider other therapies based on cost
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / determir < NPH insulin
10. Semaglutide > lixisenatide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.
† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

Fig. 32.3: American Diabetes Association (ADA) Recommendation for treatment of diabetes mellitus

- Hepatic glycogen production is also decreased.
- Rosiglitazone increases HDL, decreases LDL.
- Pioglitazone increases HDL.

Dipeptidyl peptidase-4 (DPP4) inhibitors: The enzyme DPP_4 causes rapid degradation of endogenous GLP-1 glucagon like peptide—an incretin released by gut as a result of stimulus by ingested glucose. It causes insulin release and decreases glucagon release from the pancreas and decreases appetite by activating especially, GLP-1 receptors. They have advantage of not causing hypoglycemia, no effect on weight, are safe and well tolerated. The dose of vildagliptin is 50 mg OD, saxagliptin 5 mg OD, sitagliptin 100 mg.

GLP-1 receptor agonists—is incretin secreted from gut in response to ingested glucose. It activates GLP-1 receptors and promotes insulin release, inhibits glucagon release, slows gastric emptying and suppresses appetite. The dose of exenatide is 5 µg SC BD within 1 hr of meals. Liraglutide Dose—0.6 mg daily.

Sodium glucose cotransporter-2 (SGLT-2) inhibitors: Inhibit SGLT-2 transporter present in proximal tubule. SGLT-2 is responsible for all the glucose filtered at the glomerulus to be reabsorbed in proximal tubules. Its inhibition causes glucosuria and lowers blood glucose in type 2 DM, also causes weight loss. Glycosuria can cause polyuria, polydipsia, urinary tract, and genital infection. Sodium loss may occur. The dose of canagliflozin is 100 mg oral OD before the first meal of the day. The starting dose of dapagliflozin is oral 5 mg OD, can be increased to 10 mg. They are contraindicated in renal insufficiency.

American Diabetes Association recommendations are mentioned in Fig. 32.3.

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Chapter
33

Treatment of Thyroid Disorders

The normal thyroid gland produces various hormones and secretes sufficient amounts of the thyroid hormones—triiodothyronine and thyroxine (T_4 and T_3)—to regulate body's metabolic rate, growth and development, body temperature and energy levels. It controls heart, muscle, digestive function, brain development and bone maintenance. Normal thyroid function is needed to maintain pregnancy and lactation. It stimulates cellular metabolism and increases basal metabolic rate. T_4 is facilitatory to erythropoiesis.

HYPOTHYROIDISM

Any functional or structural derangement of thyroid leads to decreased output of hormone. The clinical features of hypothyroidism depend on the age when it appears. When present during infancy, it results in cretinism with physical and mental retardation. In older children, presents as myxedema in which there is doughy thickened skin resistant to pitting. The most important laboratory investigation is increase in serum TSH. Initial clinical features are constipation, hoarse, husky cry, somnolence and failure to thrive. The abdomen becomes protuberant, skin dry and delay in appearance of the deciduous teeth accompanied by impaired skeletal growth. The fully-developed syndrome is characterized by dry rough skin, widely set eyes, retro-orbital puffiness, a flat broad nose and large protuberant tongue. There is mental retardation, sluggishness, diminished reflexes, impaired fertility, oligomenorrhea.

Treatment: Replacement with levothyroxine (thyroxine T_4) is done lifelong. In long standing hypothyroidism, in older patients and in patients with cardiac disease, it is essential to start treatment with reduced doses of levothyroxine 12.5–25 µg/day for 2 weeks. The daily dose is increased by 25 µg every 2 weeks till the euthyroid stage is reached. Thyroxine should be administered empty stomach (30 min before meals).

Myxedema coma—is a rare fatal complication of hypothyroidism with multiple organ dysfunction associated with altered sensorium. It occurs in long standing severe untreated hypothyroidism. It is characterized by clinical signs of swelling and thickness of skin, weakness, low energy and lethargy, brittle or sparse hair, cold intolerance, decreased breathing, hypothermia, hypoglycemia, hyponatremia, water intoxication, shock and death. Treatment is giving T_3 orally or IV in dose of 2.5 to 5 µg every 8 hours. O_2 therapy, monitoring of cardiac output and pressure, gradual rewarming, hydrocortisone 100 mg IV 8 hourly, glucose infusion to prevent hypoglycemia is done.

Hyperthyroidism (Graves' disease): It occurs when thyroid gland overproduces thyroid hormones. Graves' disease is the most common cause of hyperthyroidism. It is an autoimmune disorder due to circulating autoantibodies. Other causes are inflammation of the thyroid gland called thyroiditis, taking too much thyroid hormone, non-cancerous growth of thyroid gland, taking too much iodine in diet. Most striking features of hyperthyroidism are weight loss, hand tremors, heat intolerance, lid lag, upper lid retraction, weakness of eye muscles, diplopia, periorbital edema. There is anxiety, nervousness, tremors, hyperreflexia and diarrhea.

Diagnosis of hyperthyroidism: T_3, T_4 increased. TSH is suppressed, thyroid peroxidase (TPO) and thyroglobulin antibodies are present in most cases of Graves' disease.

Treatment

Antithyroid drugs: The enzyme peroxidase is inhibited by thionamides which inhibit the iodination of tyrosine residue in thyroglobulin and subsequent coupling to form T_3, T_4 hormones.

Methimazole or propylthiouracil inhibits thyroid hormone synthesis and administered until the disease undergoes spontaneous remission. Methimazole is the preferred drug due to once daily administration. The initial dose is 20–40 mg for a period of 4–8 weeks and then maintenance therapy with 5–15 mg once daily can be given. Carbimazole 20–40 mg daily.

In thyrotoxicosis during pregnancy, patient can be treated with propylthiouracil (<300 mg) in the first trimester.

Treatment—iodine and iodides (KI): High doses inhibit thyroid hormone release called thyroid constipation. They make the gland less vascular. Lugol's solution, iodide 100–300 mg/day.

Radioactive iodine: With administration of radioiodine, the gland will shrink in size and the patient becomes euthyroid after 6–12 weeks of treatment. I^{131} and I^{123} are iodine radioisotopes which are administered orally, get concentrated in thyroid follicular cell, incorporated into iodotyrosine and deposited in the colloid. They destroy parenchymal cells by β-radiation. Used in elderly patients not fit for surgery.

Subtotal thyroidectomy: Patients should be euthyroid before surgery. For this, patient is treated with antithyroid drugs for 6 weeks.

Thyroid storm: It is a rare complication of hyperthyroidism and is a medical emergency as being life-threatening. It is caused by a sudden event or illness such as surgery or infection or sudden withdrawal of antithyroid drugs or use of iodinated contrast agent for imaging. The patient presents with symptoms of high fever, agitation, delirium, loss of consciousness. The complications can be arrythmias, pulmonary edema , heart failure and death. The treatment is:

- **Beta-blocker:** Drug to control increased adrenergic tone—propranolol is administered 1–2 mg slow IV followed by 40–80 mg every 6 hrs.
- **Therapy to block peripheral conversion of T_4 to T_3:** Propylthiouracil 200–300 mg given orally 6 hourly, reduces hormone synthesis as well peripheral T_4 to T_3 conversion.
- **Therapy to reduce thyroid hormone release from thyroid:** Iaponic acid—05–1 g oral OD

- **Corticosteroids**—hydrocorticosterone 100 mg IV 8 hourly followed by oral prednisolone.
- **Diltiazem**—60–120 mg BD may be adjunctive drug if tachycardia not resolved by propranolol.
- Fluids for dehydration, vitamins, glucose, anxiolytics, cooling blankets to return body temperature to normal, and appropriate antibiotics.

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Chapter 34

Treatment of Gynecological Disorders and Obstetric Complications

The naturally active steroid hormones secreted by the ovary, adrenal gland and during pregnancy by placenta are estrogens. Estradiol is the major estrogen produced by these organs. Estrogens play active role in normal development of female genital tract, of breast and of female sex characters. Blood estrogen must be above a critical level to maintain proliferative and secretory phases of the endometrium. Estrogens also have anabolic action and are helpful in maintaining bone mass by decreasing bone resorption.

INDICATIONS OF ESTROGEN THERAPY

Primary hypogonadism: Treatment is done at 11–13 years of age in order to stimulate the pubertal changes, to stimulate optimal skeletal growth and to avoid the psychological consequences of delayed puberty and estrogen deficiency. Treatment is started with small doses of estrogens (0.3 mg conjugated estrogens or 5–10 µg ethinylestradiol) on first 21 days of each month. When growth is completed, both estrogens and progestins are coadministered.

Menopause is the time when menstruation ceases, and ovarian function ceases and there is fall in oestrogen levels leading to rebound increase in secretion of FSH. The plasma estrogen may remain low at 10–20 pg/ml. The menopausal women complaints of hot flushes and sweating, mental depression, irritability, paresthesias in the extremities. Libido is increased due to raised androgen secretion from adrenal cortex. There can be osteoarthritis, fibrositis, backache and intervertebral disc lesions, bone resorption after menopause. The vertebral bones, distal end of radius and head of femur are mostly affected. Obesity and hirsutism is seen along with hypothyroidism, raised cholesterol, brittleness of hair, reduction of mental power and concentration. There are changes in the genital tract like vulva atrophies, vagina becomes dry, cervix atrophies, ovulation ceases and ovary atrophies.

Treatment

Oestrogen therapy: Ethinyl estradiol in dose of 0.01 mg given over few months will relieve hot flushes, night sweats, palpitation and disturbed sleep. Estrogen cream is applied in cases of dyspareunia, urethral syndrome and senile vaginitis. 0.625 mg of conjugated estrogen or. 01 mg of ethinyl estradiol daily is advised to prevent osteoporosis after menopause. A progestin—medroxyprogesterone acetate 10 mg daily is advised for last 12 days in a cycle to prevent the side-effects of estrogens. The risks of estrogen therapy are postmenopausal bleeding, endometrial carcinoma, thromboembolism, liver and gallbladder disease and breast cancer.

BENEFITS OF HORMONE REPLACEMENT THERAPY (HRT)

- To decrease the everyday's symptoms of estrogen loss.
- Hot flushes
- Osteoporosis

Potential Health Risks

Breast cancer, endometrial cancers, thrombophlebitis, cyclic bleeding, breast tenderness, mood changes, and weight gain and water retention.

STANDARD THERAPY FOR TREATMENT OF MENOPAUSAL SYMPTOMS

Types of estrogen: Estrogens are marketed as oral and parenteral forms. The conjugated equine estrogens (premarin), prepared from urine of pregnant mares is the most commonly prescribed oral estrogen preparation. Switch to alternative estrogen preparation if there are side-effects with one formulation.

Estrogen alone: Estrogen therapy alone should be avoided with an intact uterus. The reasonable approach is to use the lowest effective dose of estrogen coupled with yearly surveillance of endometrium by endometrial biopsy. Otherwise daily estrogen alone can be given to women after hysterectomy.

Transdermal estradiol patches: Have been found effective methods of hormone replacement. But potential drawback is they are expensive. They are used when oral therapy does not alleviate symptoms or is poorly-tolerated.

Vaginal use of conjugated estrogens: Estrogens are absorbed by vaginal route to similar extent as that of an oral absorption. Used for atrophic vaginitis, where there is contraindication to oral therapy.

Progestins: Given orally in the doses prescribed to protect the endometrium (2.5–10 mg) daily for last 10 days of the month. Side-effects can be anxiety, irritability or depression. No single progestin is superior to another. If woman has significant side-effects with a lower dose; a different progestin formulation should be given.

Mixed estrogens and androgens preparations—containing 3–4 mg of methyltetosterone and 30–50 ug of ethinylestradiol are available for oral use. The recommended dose of estrogen is said 1–2 tab daily to prevent virilism and androgens give sensation of well-being and prevent estrogenic stimulation of breast and endometrium.

Biphosphonates: Etidronate and tiludronate reduce bone resporption by inhibiting osteoclastic activity. Alendronate and risedronate 35–70 mg weekly should be taken empty stomach in the morning with a glass of water. The patient should not lie down or take food for at least 30 minutes to prevent esophagitis. Risedronate is more potent than alendronate but equally efficacious.

Zoledronate 4 mg infused IV over 15 minutes, once every year, is useful in those not tolerating oral biphosphonates.

Selective estrogen receptor modulators (SERMS)—are estrogen agonists/antagonists acting on estrogen receptors and are tissue selective. These drugs produce estrogenic activity in those tissues where actions are beneficial, e.g. (bone, brain, liver) as during postmenopausal

hormone replacement and to have rather no activity or antagonistic activity in tissues—breast and endometrium where estrogen actions are harmful. Currently approved drugs are tamoxifen citrate 20 mg/day and raloxifene hydrochloride–60 mg/day.

Tamoxifene and raloxifene are useful in breast cancers treatment in post-menopausal women being treated with HRT. The response rates are high in tumors that are ER +ve tumors. Adverse effects include hot flushes, deep vein thrombosis and pulmonary embolism.

Progesterone is synthesized in the ovary, testis and adrenal from circulating cholesterol. Large amounts are also synthesized and released by the placenta during pregnancy. Progesterone is rapidly absorbed following administration by any route. Its uses are:

1. As *contraceptive:*
   - Combined pills—(norgestrel/levonorgestrel/desogestrel) progestins with ethinyl estradiol, 30 µg.
   - Postcoital pill—levonorgestrel 0.25 mg with ethinyl estradiol 50 µg within 72 hours of unprotected intercourse.
   - Long-acting progestin injections—depot medroxyprogesterone acetate (DMPA) 150 mg at 3 months interval. Norethindrone enanthate 200 mg at 2 months intervals. Side-effect is menstrual irregularity.
2. Hormone replacement therapy—progesterone is given for last 10–14 days of menstrual cycle every month.
3. Dysfunctional uterine bleeding—is abnormal genital tract bleeding based in uterus without any structural or organic pathology. It is due to hormonal imbalance and can be ovulatory or anovulatory. It can be treated by giving medroxyprogesterone 10–20 mg /day or norethindrone 5–10 mg /day for 3–6 months depending on the duration of bleeding. Also combined oral contraceptives can be given.
4. Endometriosis, e.g. treatment is with norethindrone acetate pills, levonorgestrel-releasing intrauterine device. It thins the lining of uterus and limits endometrial tissue growth.
5. Premenstrual syndrome
6. Threatened abortion
7. Endometrial carcinoma

Postmenopausal bleeding: The vaginal bleeding which occurs after 6 months of amenorrhea at any time after menopause is called postmenopausal bleeding. The causes are:

1. Indiscriminate use of unopposed estrogen
2. Vulvitis, trauma, lesions
3. Vagina—senile vaginitis, vaginal tunours, cancer, ring pessary for prolapse
4. Cervix—erosion, polyp, cervicitis, malignancy
5. Uterus—senile endometritis, tubercular endometritis, endometrial hyperplasia, cancers
6. Dysfunctional uterine bleeding
7. Malignancy of fallopian tube
8. Ovary—benign tumors
9. Urinary tract, urethral caruncle, papilloma and carcinoma of bladder
10. Bowel hemorrhoids, fissure, rectal cancer

Investigations: Speculum and vaginal examination to find the genital cause. BP should be checked.

Blood count and Hb should be investigated. Blood dyscrasias should be ruled out.

Cervical cytology, uterine aspiration cytology, fractional curettage to find out uterine cause. USG and laproscopy in case of pelvic mass.

If urogenital cause, cystoscopy and rectal examination to find the cause.

Treatment: Treat the cause. If the patient continues to bleed despite no cause found, do laparotomy and hysterectomy.

Amenorrhoea: It is defined as absence of menstruation. Physiological amenorrhea can be prepubertal, during pregnancy, lactation and post-menopausal. Pathological amenorrhea can be primary or secondary. When menstruation does not start by the age of 16 or in the presence of well-developed secondary sex characters, menses fails to start by the age of 14, it is called primary amenorrhea. When amenorrhea persists for 6 months or more in a woman with previous normal menstruation without pregnancy, it is called secondary amenorrhea.

Pathological primary amenorrhea can be due to:

- Congenital obstructive defects in lower genital tract.
- Congenital absence of the uterus
- Intersexualism
- Hypopituitary dwarfism
- Hypothyroid cretinism
- Delayed puberty
- Hypothalamic deficiency of GnRH
- Orgainic brain lesions–tumors, infections
- Kallman syndrome.

Pathological secondary amenorrhea can be due to:

- Acquired obstruction in the lower genital tract.

Uterine Causes

- Hysterectomy
- Destruction of endometrium—genital TB, Asherman's syndrome.

Ovarian Function

- Destruction of both ovaries by disease, oophorectomy
- Ovarian failure
- Hyperhormonal amenorrhea
- Polycystic ovarian disease
- Premature menopause
- Masculinizing tumors of the ovary.

Diseases and Disorders Affecting the Pituitary

- Psychogenic from the higher centres via thalamus and hypothalamus
- Cushing's disease
- Gigantism and acromegaly
- Pituitary failure due to chromophobe adenoma, postpartum pituitary necrosis.
- Oral pills and psychotropic drugs causing hyperprolactinemia
- Prolactinoma

- Adrenal cortical hyperplasia, adrenal cortical tumors, adrenal failure (Addison's disease).
- Thyroid—hyperthyroid status and late stages of hypothyroidism
- Diabetes mellitus
- Severe debilitating diseases like severe anemia, fulminating TB, renal disease, nutritional disorder—extreme obesity, anorexia nervosa.
- Amenorrhea due to chromosomal anomalies

Investigation and diagnosis: A thorough general examination of the patient and exclusion of systemic disease is mandatory. Patient should be screened for hyperthyroidism and hypothyroidism. In absence of secondary sex characters, pituitary infantilism or Turner's syndrome is diagnosed. Hirsutism along with amenorrhea indicates adrenogenital syndrome or a virilizing ovarian tumor or polycystic ovarian disease. Adiposity without striae and hirsutism suggest a Frohlich syndrome. Adiposity and stria suggest Cushing's syndrome. Presence of galactorrhea suggests hyperprolactinemia. A pelvic examination rules out imperforate hymen, stenosis of the vagina, stenosis of the cervix. Also the size of uterus and ovaries are assessed. Also following investigations should be done.

- X-ray of the chest to rule out pulmonary TB.
- X-ray of pituitary fossa to detect pituitary neoplasm.
- Fasting and postprandial sugar levels.
- T_3, T_4, TSH to detect thyroid dysfunction.
- Blood cholesterol estimation
- Water excretion tests and sodium and potassium estimations in case of adrenal cortical dysfunction.
- A diagnostic curettage
- Hysterosalpingography to rule out genital hypoplasia and TB.
- Vaginal smears to provide assay of ovarian function.

Hormonal assays: High FSH is found in Turner's syndrome, premature menopause and ovarian failure. Low gonadotropins are seen in hypothalamic and pituitary failure. Low FSH and high LH is seen in polycystic ovarian disease. Oestradiol level is low in ovarian failure, and in premature menopause.

17-ketosteroids excretion in urine is increased in adrenogenital syndrome.

USG of the pelvis provides an assessment of uterus and ovaries and in detection of polycystic ovaries.

Treatment: Treatment of amenorrhea is done by treating the underlying cause. Medroxyprogesterone acetate is given 10 mg daily for 7–10 days. If no withdrawl bleeding occurs, a combination of estrogen and progesterone is given for 3 days. Patient is to be investigated for any anatomical abnormality (synechia etc.) if there is no bleeding after combination therapy. Assurance and proper guidance will help the woman with secondary amenorrhea due to ovarian and pituitary failure.

Premenstrual tension: Before the onset of menstruation, 7–10 days before, many women experience premenstrual symptoms like irritability, malaise, headache, gastrointestinal upsets such as colon spasm and constipation, frequency of micturition, and a feeling of fullness in the breasts, abdomen, face and feet. All these symptoms become exaggerated and turn into a psychosomatic disorder in introspective and neurotic women The phenomenon is due to

excess estrogen production, adrenal cortical steroids and progesterone causing an increase in extracellular water throughout the body.

Treatment: Limited water intake and a salt free diet for 10 days preceding menstruation is recommended. Saline purgatives, ammonium chloride and chlorothiazide in a single dose of 250 mg from the onset of symptoms until menstruation sets in, are useful. For congestion of breasts, adequate support is essential and for menstrual migraine–ergotamine tartrate is best treatment10 mg maximum.

Menorrhagia: It is defined as profuse menstrual blood flow with intact menstrual cycle. It is caused by any condition that increases the surface area of menstruating endometrium. e.g. fibroids, endometrial polyps, or any pelvic inflammatory disease. Severe anemia, psychological disorders, emotional upset, matrimonial disharmony and anxiety are important factors. In hyperthyroidism and myxoedema, menorrhagia can occur.

Classification

Anovulatory

- Threshold bleeding of puberty menorrhagia
- Metropathia hemorrhagica
- Premenopausal dysfunctional uterine bleeding.

Ovulatory

- Irregular bleeding
- Irregular shedding
- IUCD insertion
- Following sterilization operation.

Puberty menorrhagia is a threshold bleeding of adolescence caused by excess or unopposed estrogen and absence of progesterone in the anovulatory cycles. Estrogen therapy gives good results. Progesterone and OCPs are used during an episode of bleeding. If a girl fails to respond to hormonal therapy, curettage of endometrium is necessary to rule out genital TB.

Premenopausal menorrhagia is seen in women with anovulatory cycles. Otherwise conservative therapy with medroxyprogesterone 200 mg orally twice daily or 17-alpha hydroxy progesterone 1 g weekly for 6 months to a year is prescribed. Progesterone therapy avoids the risk of malignancy and obviates the need of hysterectomy. Dilatation and curettage can cure 30–40% cases of menorrhagia, otherwise hysterectomy is advised.

Diagnosis of Menorrhagia

A detailed history of onset of bleeding, its duration and amount of blood, its character and cyclical features, antecedent cause such as IUCD, recent delivery and abortion, is asked.

A full general examination, including thyroid dysfunction tests, a full blood count followed by a bimanual pelvic examination.

A diagnostic curettage.

USG to exclude extrauterine pathology.

Conservative treatment: Under forty, the treatment is essentially conservative. In any patient suffering from severe dysfunctional bleeding, oral iron is given to correct anemia.

Rest, sedatives and reassurance should be given during a severe bout of bleeding.

Hormone therapy: The newly active progestational steroids as norethynodrel, norethisterone or lynestrenol are safer than estrogen. A high initial dose of 10–30 mg a day arrests bleeding in 24–48 hours followed by 5 mg a day for 20 days is given. Withdrawal bleeding occurs after 2–5 days of cessation of treatment. Treatment is continued for 3–6 months. Duphaston (dihydrogesterone) 10 mg tab/day from 11th to 25th day of cycle does not suppress ovulation and is useful in young women desirous of pregnancy.

Combined OCPs are useful in menorrhagia if a woman does not require pregnancy. It is more effective than oestrogen or progesterone alone.

Metropathia hemorrhagica—is a specialized dysfunctional uterine bleeding in which the endometrium of the uterus is thick and polypoidal and one or the other ovary contains a cystic follicle. The disease is most prevalent in women >40 and the most common complaint is of confirmed vaginal bleeding which may last for many weeks. The bleeding is always painless as it is anovulatory. Treatment is by nor-ethynodrel, norethisterone and lynestrenol. Continuous heavy bleeding is treated by giving 5–10 mg of progesterone tds daily till bleeding ceases. It is followed by maintenance dose.

Dysmenorrhoea: Some degree of discomfort is usual during normal menstruation but the pain of spasmodic dysmenorrhea develops typically on the first day of the period of bleeding. It is marked by severe pain in abdomen which may cause fainting and vomiting and forcing the patient to lie down. This type of pain lasts for more than 12 hours followed by usual abdominal discomfort which persists but decreases throughout the period of bleeding. In congestive dysmenorrhea, the patient complains of a dull pain in the back and in lower abdomen which begins a few days back before the onset of menstrual flow and is relieved by bleeding, though a feeling of heaviness in the pelvis may continue throughout the duration of loss.

Treatment: Spasmodic dysmenorrhea is usually cured by pregnancy.

The management includes explanation of menstrual process, sex education and reassurance to the patient.

The woman is advised to have nourishing diet. The correction of constipation, physical exercise and inculcating regular habits are necessary adjuvants.

Simple analgesics like baralgan and buscopan, hyoscine bromide tablets are useful in dysmenorrhea. PG synthesis inhibitors diminish myometrial activity and relieve pain of dysmenorrhea. Mefenamic acid oral tds 250 mg, indomethacin 50 mg or naproxen sodium 50 mg. Headache, gastrointestinal symptoms, blurred vision, diminished menstruation, acute renal disease are the side-effects of prolonged use of these drugs.

Vaginal discharge: In healthy women, the vagina contains a small quantity of watery secretion containing mucus, desquamated epithelial cells, doderlein's bacilli and lactic acid. A physiological discharge occurs at the time of ovulation, as a result of sexual stimulation, premenstrual congestion, during pregnancy. In case of pathological discharge, patient should be asked about the nature, colour, duration, whether it is offensive and blood stained. Infection due to *Trichomonas* and *Candida* causes considerable itching. Blood-stained vaginal discharge is due to lesion in the lower genital tract, especially the cervix. Offensive discharge is due to secondary infection by bacteria.

In *Trichomonas vaginitis*, the vaginal discharge is profuse, thin, creamy or slightly greenish, irritating and frothy. The treatment is done by metronidazole 200 mg TDS oral for 7 days. The recurrence of infection suggests that the partner should also receive treatment as the disease is sexually transmitted.

Moniliasis is due to Gram-positive fungus, *Candida albicans*. There is profuse curdy discharge and intense pruritis. Treatment is with miconazole, clotrimazole vaginal pessaries or vaginal creams. Ketoconazole is available as vaginal pessary, ointment for external use and oral pills.

Chlamydia trachomatis is an obligate intracellular parasite. It causes lymphogranuloma venereum and other non-LGV which causes nonspecific lower genital infection. Often the woman is asymptomatic but may develop vaginal discharge, dysuria and frequency of micturition. Tetracycline and clindamycin 500 mg 6 hourly for 14 days are found effective. The combination of cefoxitin and ceftriaxone with doxycycline (100 mg BD × 14 days) is also helpful.

Fibromyomas are benign neoplasms and are well-circumscribed tumors of smooth muscle cells and interlacing fibrous tissue connective cells, firm in consistency. The myomas mostly arise in the uterus but they also arise from the round ligament, the utero-ovarian, uterosacral ligaments, the vagina and at the vulva. The presence of myoma causes hyperplasia of the myometrial wall and secondary changes can occur including degenerations, fatty changes with other complications like torsion, inversion of the uterus, capsule rupture, inflammatory changes in the myoma and may result in endometrial carcinoma in 3% cases. Infertility is caused by submucous myoma distorting the cavity of the uterus. The symptoms include menorrhagia, polymenorrhoea, metrorrhagia, spasmodic dysmenorrhea, pressure symptoms like–difficulty in micturition and constipation. There can be blood-stained discharge in myomatous polyp and anemia caused by menorrhagia. The physical signs include abdominal distension below the umbilicus and on palpation a tumor is found arising from the pelvis, firm with smooth surface. The cervix moves with the swelling and uterus cannot be felt separate from the mass. It is movable from side to side, not tender unless torsion or malignancy has occurred.

USG in useful is establishing the diagnosis. Immediate treatment is not necessary in case of symptomless myomas. Symptomless myomas are usually of subserous type. Treatment is necessary in case of excessive hemorrhage or because of pressure symptoms.

Conservative treatment: The profound anemia is treated by giving blood transfusion.

Danazol—androgenic and anti-estrogenic given orally 400–800 mg daily for 3–6 months reduces the size of tumor as seen by USG.

Synthetic GnRH analog given subcutaneously—200 µg daily or intranasally 300–400 ug tds daily for 6 months reduces the size of myomas.

The other alternatives are myomectomy in which tumors are removed and total hysterectomy, when uterus containing myoma is removed.

Pelvic inflammatory disease: Inflammation of upper genital tract involving the fallopian tubes as well as ovaries. It can be due to sexually transmitted diseases such as gonococcal, chlamydia, mycoplasma, tubercular bacillus, viruses. aerobes, anaerobes. Dilation and curettage and hysterosalpingogram, IUCD insertion, pelvic peritonitis can cause ascending infection.

Symptoms and signs: The commonest symptom is abdominal pain induced by pelvic infection and by swollen appendages. Pain is bilateral and restricted to lower abdomen. The patient is febrile with high temperature. Vomiting occurs in severe cases. Menstrual irregularities are common.

Diagnosis: Abdominal examination shows distension combined with tenderness and rigidity in the lower abdomen. In an acute stage, cervical movement tenderness and tenderness in fornices are the only evidence of pelvic infection. In milder form, tender pelvic masses in the lateral fornices are evident. A pelvic abscess produces a fluctuating tender swelling in the pouch of doughlas, bulging into posterior fornix and the patient develops severe diarrhoea.

Treatment: Rest and IV fluids in case of dehydration and vomiting. Analgesics are needed. Antibiotic therapy for both aerobes and anaerobes. Surgical treatment is needed in case of chronic PID. Almost 15% suffer from infertility and 8% of those who conceive will have an ectopic pregnancy.

Abortions: Expulsion of products of conception either spontaneous or induced before viable age of 28 weeks gestation is defined as abortion. Abortions can occur due to chromosomal anomaly, trauma, abnormalities of placenta and membranes, general diseases of the mother—malaria, typhoid fever, chronic infections like toxoplasmosis, mycoplasma hominis, genital herpes and plasma urealyticum. Hypertension, like chronic nephritis can cause abortion by interfering with placental circulation and fetal O_2 supply. Local abnormalities of the genital tract like bicornuate uterus, septate uterus, fibromyomas, cervical incompetence, disturbances of endocrine system, psychological disturbances, faults in gametes, smoking, and alcohol can be the causes of abortions.

The types of abortions are classified as:

Threatened abortion: During early weeks of pregnancy, there is slight painless vaginal hemorrhage accompanied by discomfort. On examination, blood is discharged through cervical canal but OS is closed. USG shows an intact gestation sac corresponding to the period of amenorrhea. After 10 weeks, fetal movements and fetal heart rate are discernible, indicating fetus is live. A low-lying placenta associated with threatened abortion can be detected.

Treatment: Rest till bleeding ceases. Coitus is prohibited. Sedation with morphine, pethidine or calmpose helps to allay anxiety. Uterine relaxant like isoxsuprine hydrochloride is useful. 17-Hydroxyprogesterone is safe in pregnancy and not continued beyond 20 weeks but ultrasound should rule out blighted ovum or missed abortion first.

Inevitable abortion: There is severe vaginal bleeding with painful uterine contractions. In the second trimester, the confirmation sign is rupture of membranes and the drainage of liquor amnii.

Treatment: In a process of abortion, IV or IM inj. of 0.2 mg methergine and also syntocinon (oxytocin) in IV drip will reduce the bleeding and expedite the process of expulsion.

Missed abortion: After amenorrhea of pregnancy, there may be no continued enlargement of the breasts, abdomen and after several weeks a brownish discharge develops, uterus contracts and expells the ovum. On examination, uterus is soft and shrinks in size not corresponding with the period of amenorrhea and the OS is closed. The presence of a dead fetus or a blighted ovum can be confirmed by USG. After 10 weeks of gestation, absence of fetal movements and fetal heart activity indicate dead fetus.

Evacuation is done in all cases of abortions except threatened abortions.

Induced abortion: Mifepristone has antiprogestational, antiglucocorticoid and antiandrogenic activity. It slows follicular development and causes failure of ovulation. Also, it blocks progesterone support to the endometrium and if implantation occurs, it dislodges the conceptus leading to abortion. 600 mg single oral dose followed up 48 hours later by a single 400 μg oral dose of misoprostol, is used to induce abortion of upto 7 weeks pregnancy.

Polycystic ovarian disease (Stein-Levinthal syndrome)

It is seen in young women characterized by secondary amenorrhea, infertility, obesity, hirsutism and acne. Both the ovaries enlarge up to 3 times the normal size and ovaries contain many cysts. Treatment is by giving birth control pills. Electrocoagulation of cysts is also done. Also lifestyle modification helps in attention to diet, exercise and weight loss.

Endometriosis is the occurrence of endometrial tissues at ectopic sites outside the true cavity of the uterus. This disease occurs during childbearing age and is frequently associated with infertility. The common ectopic sites are the ovaries, the uterosacral ligaments, peritoneum overlying the bladder, sigmoid colon, back of uterus, intestinal coils and appendix. Chocolate cysts of ovaries most commonly can result. The symptoms are secondary dysmenorrhea, backache, low abdominal pain, dyspareunia, infertility, menorrhagia, urological symptoms (frequency and dysuria). Abdominal examination may reveal a cystic swelling in case of chocolate cyst of ovary. Blackish puckered tender spots in the posterior fornix are seen on speculum examination.

Treatment: Danazol is mildly anabolic, anti-oestrogenic and antiprogestational 200–800 mg daily for 3–6 months. The lesions regress remarkably but side-effects like weight gain, hirsutism, excessive sweating, depression, atrophy of breasts and vaginitis can occur.

GnRH (Buserelin nasal spray, goserelin, leuprolide monthly inj. SC) is administered continuously for 3–6 months to suppress pituitary gonadotropins and reduce estrogen levels (cause atrophy of endometriotic tissue).

Adenomyosis is a common condition in elderly women in which islands of endometrium are found in the wall of the uterus. The disease often exists with uterine fibromyoma and endometrial carcinoma. These women are parous, around 40 years and present with menorrhagia and progressively increasing dysmenorhea. Pelvic discomfort, backache and dyspareunia are other symptoms. If the adenomyosis is diffuse, there is symmetrical enlargement of uterus on clinical examination. Treatment is diagnostic hysteroscopy with curettage. In elderly women, not desirous of child bearing, total hysterctomy is the correct treatment.

Infertility means failure of a couple to conceive after one year of unprotected and regular intercourse.

The causes can be:

- Defective spermatogenesis
- TB of fallopian tubes
- Hypothyroidism
- Failure of ovulation.

Investigations: Serum TSH, LH, FSH, antimullerian factor, serum prolactin, hysterosalpinogography to rule out TB of fallopian tubes. Transvaginal ultrasound (TVS) study to watch for ovulation.

Treatment

Clomiphene citrate: It acts as pure estrogen antagonist in all human tissues. It promotes secretion of gonadotropins (Gns). The LH /FSH secretion increases and ovaries enlarge to cause ovulation. 5 mg once daily dose is given for 5 days starting from 5th day of cycle. The daily dose can be doubled if no conception occurs for 2–3 cycles. It is also used to aid i*n vitro* fertilization when given with Gns. It causes synchronous maturation of several ova to cause ovulation. In men, it increases Gns secretion, promotes spermatogenesis and testosterone secretion. 25 mg daily for 24 days in a month with 6 days abstinence up to 6 months is advised.

When there is deficient production of Gns by pituitary, it is advised to give 1 inj. of menotropins (75 IU FSH + 75 IU LH or 75 pure FSH) IM daily for 10 days followed next day by 10, 000 IU of HCG. Ovulation occurs within 24–48 hours and the women may conceive. In *in vitro* fertilization, endogenous FH/LH are suppressed by continuous pretreatment with a superactive GnRH agonist—nafarelin 400 µg BD intransal or goserelin as a depot SC/IM inj., followed by ovarian hyperstimulation.

Hyperprolactinemia occurs due to microprolactinomas leading to galactorrhea, amenorrhea and infertility in women, gynecomastia, impotence and sterility in men. Treatment is done with bromocriptine and cabergoline as first line drugs. Bromocriptine is D_2 agonist which decreases prolactin release from pituitary at dose 2.5 to 10 mg/day. It causes nausea, vomiting, postural hypotension and lately behavioral alterations, mental confusion, hallucinations. Cabergoline is more D_2 selective and longer acting and given twice weekly at dose of 0.25–1 mg.

Fibrocystic breast disease: Danazol is an impeded androgen causing suppression of Gn secretion from pituitary. 3–6 months treatment decreases pain, nodularity and engorgement in most of the cases. 200 mg BD for 3–6 months.

Antenatal Assessment and Treatment

Total antenatal visits are 4 —first visit 6–9 weeks for presence of fetal heart sound, second visit at 14 weeks for anomaly scan, third visit at 28 weeks to rule out glucose tolerance test, hypertension, threatened abortion and fourth visit at 37 weeks to find baby weight, presentation, engagement of presenting part.

Tetanus diptheria vaccine is given to the mother at first visit.

In case of threatened abortion, empirical treatment is given like microionised progesterone oral 200 µg to 400 micrograms up to 14 weeks. After 14 weeks, proluton depot (hydroxyprogesterone caproate), 500 IU IM injections oil based every week are given till 35 weeks.

Bed rest and inj. tranexa is advised.

For medical illnesses during pregnancy, following treatment is given:

- Single dose metrogyl in diarrhea, inj. ceftriaxone for typhoid, tab. ciplox for UTI, tab. omeprazole, rantac can be given for acidity and heartburn.
- Tab. augumentin, ceftum, azithromycin, amoxycilin can be given in respiratory infections. For vomiting, tab. doxylamine 10 mg 1–0–2 can be given.

Pre-eclampsia and eclampsia: Pregnant hypertensive women with diastolic BP >100 are treated with the drug labetolol 100 mg twice daily with escalating doses at weekly ntervals, reaching a maximum of 1.2 g in 24 hours. During severe hypertension, patient is advised to restrict protein diet. In women with impending eclampsia, magnesium sulfate regime by intravenous or intramuscular route is administered. The intravenous regimen is 4 g dose, followed by a maintenance infusion of 1–2 g/hour. It is required to monitor respiratory rate, urine output and deep tendon reflexes. If these are normal alternative treatment is 5 g IM $MgSO_4$ is given in alternate buttocks. It is repeated 4 hourly till patient delivers 24 hours after the last fit. Monitoring is done to keep BP <140/90 mm Hg.

Premature labour is defined as one where the labour starts before the 37th completed week, counting from first day of the last menstrual period. The preterm delivery indications observed are leaking per vaginum, painful uterine contractions at least once in 10 min and lasting for 30 sec or more with progressive dilatation and effacement of cervix. In preterm labor, duvadilan 40 mg in 500 ml Ringer lactate at 8 drops/min is administered. It is isoxsuprine which is vasodilator and uterine relaxant. Glucocorticoids are administered to the mother in pregnancy less than 34 weeks at it helps in fetal lung maturation to prevent respiratory distress syndrome. Inj. betamethasone is given 12 mg IM every 12 hours for 2 doses. The glucocorticoids are contraindicated in premature rupture of membranes with evidence of infection. The preterm deliveries are delivered vaginally if cervix is favorable with good progression of labour but artificial rupture of membranes is not done. Some are terminated by cesarian section to prevent asphyxia and birth trauma.

Gestational diabetes: A glucose tolerance test is done between 24 to 28 weeks of pregnancy. The periodic checkup of fasting blood sugar level should be done which should be less than 110 mg%. The control of high blood sugar is done by restriction of diet or insulin. To control diabetes, 5% dextrose drip is started with 10 units of soluble insulin at postmeal sugar more than 150 mg%.

Placenta previa is a condition when the placenta is implanted partially/completely over the lower uterine segment and or adjacent to internal OS. It is characterized by painless and recurrent vaginal bleeding and confirmed by ultrasound. Expectant treatment is done by advising bedrest, supplementary hematinics and blood loss replaced by adequate blood transfusion. Cesarian section is advised for women with placenta previa.

Postpartum hemorrhage (PPH) is severe vaginal bleeding after childbirth. It is a serious condition that can lead to death. The causes are uterine atony, genital tract lacerations, retained placenta, uterine inversion, abnormal placentation, and coagulation disorders. If PPH is due to uterine atony, treatment is as follows:

- Oxytocin infusion 10 U in 500 ml NS stat @15 drops/min.
- Ergometrine 25 mg, IV.
- 15-methyl $PGF_{2\alpha}$ 250 µg IM, can be repeated.
- PGE1 tablet (misoprostol) 200 µg, sublingual or rectally.
- Tranexamic acid 1g IV

  If not controlled, surgical methods are explored and used.

CARE IN NEONATAL INTENSIVE CARE UNIT (NICU)

Care of preterm babies is done by resting them in incubators where temperature and humidity can be better stabilized by double walls. For prolonged O_2 delivery, the baby's head is kept

in an oxygen hood box. For maintaining airway, some of the neonates need endotracheal intubation and mechanical ventilation. Ventilatory status is monitored by blood gas sampling at regular intervals. Serum bilirubin is maintained <10 mg/dl. Antibiotic therapy is given as prophylaxis when babies were born following premature rupture of membranes—cefotaxime 50 mg/kg 12 hrly IV and amikacin 10–15 mg/kg to be given IV in 2 divided doses for 5–7 days. IV fluids were given to babies weighing less than 1200 g and gradually tube feeding is initiated after 1–3 days and then gradually moved onto spoon and breastfeeding. Fluid given is 60–80 ml/kg/day of dextrose water or breast milk 10–20 ml/kg/day on first day and increased by 15 ml/kg/day. Babies with asphyxia neonatorum have non-establishment of satisfactory pulmonary respiration at birth. The NICU in the study setting should be adequately equipped with resuscitation facilities and drugs. All babies born to diabetic mothers are checked for blood glucose within 2 hours of birth to avoid problems of hypoglycemia (blood glucose <35 mg/dl). Early breastfeeding within half to one hour is advocated and is repeated at 3–4 hourly intervals to minimize hypoglycemia and hyperbilirubinemia.

An aminodrip is also suggested for nutrition in pregnancies with intrauterine growth restriction (IUGR). The vasodilators like isoxsuprine is used to increase the blood flow in the maternal vessels supplying the placental bed.

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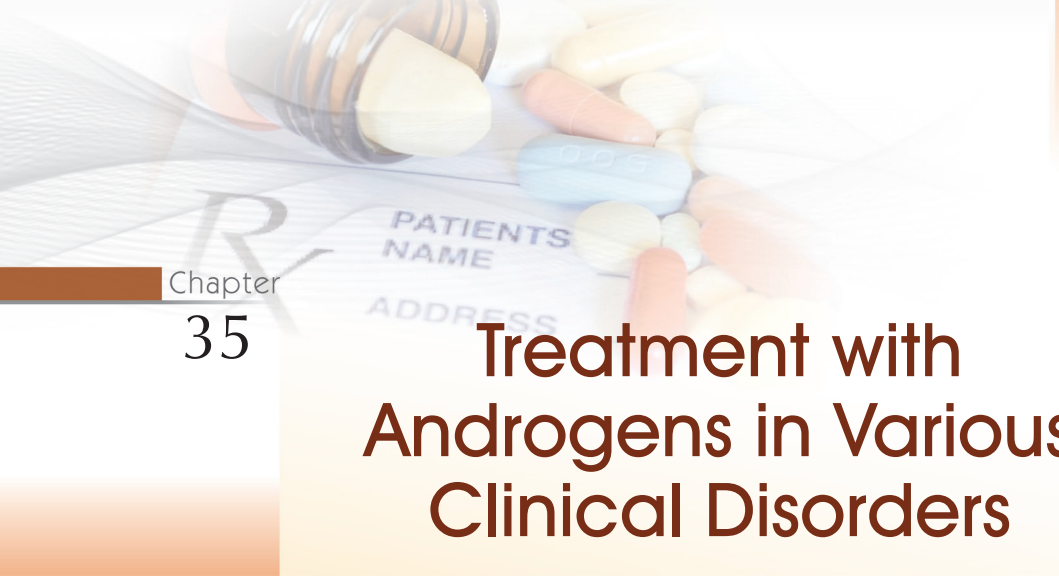

Chapter
35

Treatment with Androgens in Various Clinical Disorders

Androgens include all natural as well as synthetic steroidal drugs having masculinizing properties. Androgens are male sex hormones that cause development of male reproductive system and secondary sexual characteristics. They also maintain body protein and integrity and development of brain capabilities and male behavioural setup. Testosterone is a 10-carbon steroid hormone, synthesised from cholesterol in the leydig cells of testes, but also by adrenal cortex and the theca cells. The androgens are required for (1) normal maturation in the male, (2) sperm production, (3) increased synthesis of muscle proteins and Hb and (4) decreased bone resorption.

THERAPEUTIC USES OF ANDROGENS

- Drugs with higher androgenic effect are preferred for androgen replacement (treating hypogonadism) whereas drugs with more anabolic effect are used for treating anemia, protein loss.
- Replacement therapy in male hypogonadism, moderately useful in increasing libido and sexual performance in men who have testicular failure. Sildenafil, tadalafil, vardenafil are selective PDE 5 inhibitors useful in patients with erectile dysfunction. Sildenafil improves artenial oxygenation and used in pulmonary hypertension. The dose is 20 mg TDS.
- In female hypogonadism, in prepubertal females with hypopituitarism.
- Low doses of androgens are used to improve loss of sex drive in postmenopausal women. They also reduce postpartum breast engorgement.
- Treatment of anemia: Natural androgens stimulate erythrocyte production and used to treat refractory anemia such as aplastic anemia, hemolytic anemia and sickle cell anemia. Oxymetholone 150 mg/day PO, testosterone 150 mg/week IM for 6 months.
- As growth stimulators: Androgens promote linear growth and if used carefully, children achieve their expected adult height.
- Attacks of hereditary angioneurotic edema can be prevented by methyltestosterone or stanazolol 0.5–2 mg/daily by increasing the production of complement C1 inhibitor.
- Use as protein anabolic agents: Drugs like methadienone, nandrolone, oxymetholone and stanozolol are synthetic 19 nortestosterone derivatives, which possess a high degree of anabolic activity.
- Their use is in catabolic illnesses: Acute illness, severe trauma and major surgery nandrolone 0.4 mg/kg. They are used in osteoporosis, suboptimal growth in boys, in hypoplastic, hemolytic and malignancy associated anemia, to enhance physical activity in athletes.

- Ageing—improve bone mineralisation and muscle mass.
- Testosterone therapy is used in AIDs patients to improve weakness and muscle wasting where testosterone levels are low.

ADVERSE EFFECTS

- Androgen administration in normal males inhibits the release of FSH and LH due to negative feedback mechanism. If the administration is continued, spermatogenesis is hampered causing oligozoospermia and infertility.

Fluoxymesterone can cause cholestatic jaundice and benign liver tumors. Children receiving vigorous treatment with anabolic steroids can develop early pubertal changes with dwarf stature due to closure of epiphyses.

Impeded Androgens/Antiandrogens

- **Flutamide:** Androgen receptor antagonist used in metastatic carcinoma prostate. 250 mg TDS.
- **Finasteride** is 5-alpha reductase enzyme inhibitor which converts testosterone into more active dihydrotestosterone. It is effective orally, useful in benign hypertrophy of prostate. 5 mg OD for 6 months. Also effective in male pattern baldness.

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Chapter
36

Treatment of Adrenal Hormones Disorders

The adrenal cortex produces several hormones like aldosterone (a mineralocorticoid), cortisol (a glucocorticoid), and androgens and estrogen (sex hormones). The adrenal medulla secretes cathecolamines—adrenaline and noradrenaline involved in fight or flight response. Glucocorticoids have dose-related effects on carbohydrate, protein and lipid metabolism. The mineralocorticoids have salt retaining activity.

CLASSIFICATION

Glucocorticoids

- Short acting $t_{1/2}$ ≤12 hours, hydrocortisone
- Intermediate acting, $t_{1/2}$ = 12–36 hours, prednisolone, methylprednisolone, triamcinolone, Deflazacort.
- Long acting, $t_{1/2}$ ≥36 hours, dexamethasone, betamethasone
- **Mineralocorticoids:** Desoxycortocosterone acetate (DOCA), fludrocortisone, aldosterone

Pharmacological actions: The glucocorticoids are potent antinflammatory and immunosuppressive agents. They have catabolic activity in lymphoid tissue and connective tissue, muscle, peripheral fat and skin. Glucocorticoids stimulate gluconeogenesis and glycogen synthesis in the fasting state. The glucocorticoids increase serum glucose levels. They increase protein degradation and decrease protein synthesis. They are used to treat inflammatory, allergic and immunological disorders. Mineralocorticoids cause sodium and water retention and potassium excretion and hypokalemic alkalosis.

Uses: These can be administered parenterally, orally, topically or by inhalation. Glucocorticoids have important effects on the development of fetal lungs. Glucocorticoids are agents used for treatment of many local inflammatory, immunological, hematological disorders. Inhaled glucocorticoids such as beclomethasone dipropionate and beclomethasone valerate, fluticasone provide an alternative to systemic steroids in the treatment of chronic asthma. Therapeutic uses of steroid hormones are given below.

Replacement Therapy

1. Chronic adrenal insufficiency (Addison's disease)—adrenal glands make too little cortisol. Symptoms are extreme fatigue, weight loss and loss of appetite, areas of darkened skin, hypotension, salt craving, hypoglycemia, abdominal pain, muscle and joint pain,

irritability, depression. In primary adrenal insufficiency—20–30 mg of hydrocortisone must be given daily.
Fludrocortisone—dose—50–200 µg/day.
DOCA—dose—10–20 mg IM once weekly.

2. Acute adrenal insufficiency: Adrenal glands make too little cortisol. It can be life-threatening. Hydrocortisone sodium succinate in the dose of 100 mg IV 8 hourly until patient revives. A salt containing fludrocortisone should also be added.
3. Anti-inflammatory therapy: In arthritides, eye diseases, bronchial asthma
4. Leukemia
5. Shock
6. Congenital adrenal hyperplasia
7. Collagen diseases—lifesaving
8. Autoimmune diseases
9. Infective diseases—severe forms of TB, *pneumocystis carinii* pneumonia
10. For diagnostic purposes, e.g. dexamethasone suppression test
11. For transplant rejections because of immunosuppression.
12. Stimulation of lung maturation in fetus.

Drugs used in treatment of adrenocortical abnormalities:

Corticotropin, metyrapone, cosyntropin, aminoglutethimide, miotane, mifepristone and dexamethasone.

Adverse Effects

Patients receiving daily doses of hydrocortisone or more for longer than 2 weeks develop iatrogenic Cushing's syndrome. In the face, roundness, puffiness, fat deposition, plethora, moon facies usually appear. Adrenal suppression also occurs when corticosteroids are administered for more than 2 weeks.

Other adverse effects are hyperglycemia, hypertension, hypokalemia, peptic ulcer, osteoporosis, insomnia, cataract, fluid and electrolyte disturbances, weight gain, muscle weakness, polyuria, kidney stones, osteoporosis with fractures, and avascular necrosis of bone. Corticosteroids should be administered only when absolutely indicated for more conservative measures. The dosage and duration has to be kept to minimum. for adequate treatment. Steroid tapering is done by slowly decreasing a steroid dose overtime to prevent withdrawl and to stop inflammation from coming back.

Contraindications: Peptic ulcer, heart disease, hypertension, infections, psychosis, diabetes and osteoporosis.

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Chapter
37

Treatment of Malaria

PATHOPHYSIOLOGY

Malaria is a transmissible disease infected by a parasite transmitted from humans-to-humans by the bite of female anopheles mosquito. Four species of parasite Plasmodium in humans are—*P. vivax*, *P. ovale*, *P. malariae*, and *P. falciparum*. Malaria continues to be endemic in many parts of the tropics and subtropics. The female anopheles mosquito becomes infected by ingesting infected blood—the sexual forms of the parasite, plasmodium. The plasmodium develops in the mosquito and is inoculated into the humans on mosquito bite. The first stage of Plasmodium development in human (schizonts) takes place in the liver. The more mature Plasmodium (merozoites) escape from the liver and enter bloodstream infecting RBCs. They multiply causing RBCs to burst open after 2–3 days to release a new crop of parasites. The cycle of invasion, multiplication and RBC rupture may be repeated many times (Fig. 37.1).

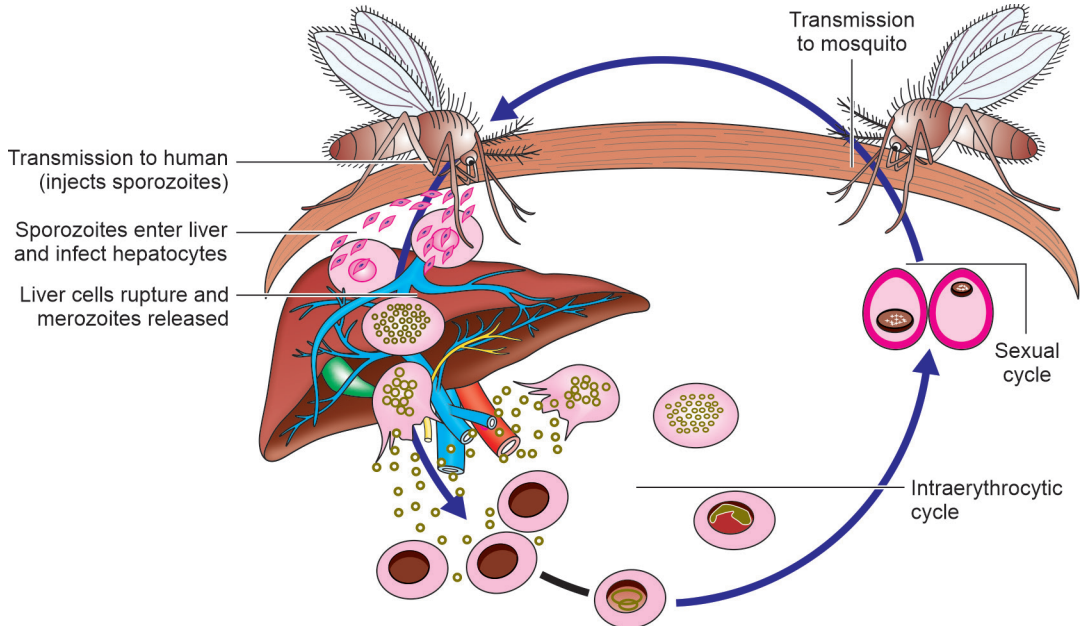
Transmission to mosquito
Transmission to human (injects sporozoites)
Sporozoites enter liver and infect hepatocytes
Liver cells rupture and merozoites released
Sexual cycle
Intraerythrocytic cycle

Fig. 37.1: Life cycle of malaria parasite

SYMPTOMS

The patient has malarial attacks present over 4–6 hours, with shaking chills, high fever and sweating and are associated with fatigue, vomiting, abdominal cramps, muscle or joint pain and backache. If the infection is caused by *P. falciparum*, cerebral malaria and death can occur within 24 hours.

Diagnosis of malaria includes following criteria:

- Complete medical history of symptoms.
- Physical examination.
- Blood tests—thick and thin blood film.

TREATMENT

The effectiveness of antimalarials varies for different species of the parasite and with different stages of the parasite's lifecycle. The drugs used for treatment of acute attack are chloroquine, quinine, primaquine, pyrimethamine and sulfadoxine. For prophylaxis, the drugs used are chloroquine, proguanil, mefloquine, pyrimethamine and dapsone.

The aim of using drugs to treat malarial infection is:

- To prevent and treat the symptoms of malaria attack.
- To completely eliminate the parasite from the patient's body.
- To lower the human reservoir of infection, cut down transmission to mosquito.

Antimalarials that act on erythrocytic schizonts are known erythrocytic schizonticides. Those that act on pre-erythrocytic as well as exoerythrocytic stages in liver called tissue schizonticides. Those which kill gametocytes in blood are called gametocides. Antimalarials are given in the following way:

Regimens Used

- Chloroquine 600 mg stat followed by 300 mg after 8 hours, and 300 mg daily for next 2 days. The pediatric dose of chloroquine is 10 mg/kg stat followed by 5 mg base/kg after 12 hours. If child vomits within ½ hour, repeat the dose.
- Total dose for infant = 150 mg. Chemoprophylaxis is done with 5 mg/kg weekly.
- Pyrimethamine 25 mg + sulfonamide 500 mg tab for chloroquine-resistant cases.

For chloroquine-resistant area: Mefloquine or doxycycline is given in the dose of 2 mg/kg daily. For chloroquine resistant + multiresistant *P. falciparum*, mefloquine 750 mg followed by 500 mg every 12 hours.

- Quinine 600 mg TDS for 7 days alone or with pyrimethamine.
- Artesenuate 100 mg BD on first day followed by 1000 mg for 5 days.

The WHO has approved following: Artemesinin based combination treatment (ACT regimen) for acute uncomplicated *P. falciparum* malaria.

1. Artesenuate 100 mg BD for 3 days + sulfadoxine 1500 mg and pyrimethamine 75 mg as single dose.
2. Artesenuate 100 mg BD for 3 days + mefloquine 15 mg/kg (750 mg) on second day, on third day 500 mg.
3. Dihydroartemesinin 120 mg + piperaquine 960 mg for 3 days.
4. Aetemether 80 mg BD + lumefantrine 480 mg BD for 3 days. Taken with fatty meal.
5. Artesenuate 200 mg + amodiaquine 600 mg daily for 3 days.

Advantages of ACT are rapid cure, recrudescence is very low, prevention of selection of resistant strains, regimen is well-tolerated with good patient compliance.

Disadvantages—are of high cost and potential toxicity.

Severe and complicated falciparum malaria is characterized by hyper parasitemia, hyperpyrexia, fluid and electrolyte imbalance, acidosis, hypoglycemia, CVS collapse, jaundice, severe anemia, spontaneous bleeding, hemoglobinuria, renal failure and cerebral malaria. IM/IV drugs are used.

1. Artesenuate 2.4 mg/kg IV/IM followed by same dose after 12 and 24 hours.
2. Artemether 3.2 mg/kg IM on first day followed by 1.6 mg/kg daily for 7 days.
3. Arteether 3.2 mg/kg IM on first day followed by 1.6 mg/kg daily for next 4 days. Then switch to oral ACT for 3 days.

PROPHYLAXIS OF MALARIA

1. Chloroquine sensitive plasmodial species: Chloroquine 300 mg base/week, start 1 week before entering endemic area and continue for 4 weeks after leaving endemic area.
2. Atovaquone 250 mg + proguanil 100 mg
3. Mefloquine 250 mg/week 1–2 weeks before entering endemic area and 4 weeks after leaving.
4. Doxycycline, 100 mg/day, 1 day prior to exposure and continue 4 weeks after leaving endemic area.

Other preventive measures include prevention of breeding of mosquito, putting on clothes that cover the body, insecticide spray, use of mosquito repellent cream and mosquito nets.

The drugs used in malaria are discussed below:

Chloroquine: It is rapidly acting erythrocytic schizonticide against all species of plasmodia and controls clinical attacks in 1–2 days. Oral absorption is excellent, its accumulation in retina is responsible for Bull's eye maculopathy. Prolonged use leads to loss of vision. Loss of hearing, rashes, photoallergy, mental disturbances, myopathy, graying of hair occur on long term use. It is not given with mefloquine, amiodarone, and other antiarrhythmics.

Chloroquine, amodiaquine, quinine, quinidine, mefloquine get concentrated in the food vacuole of sensitive plasmodium and increase the pH and inhibit the peroxidation of heme into hemozoin. Inactivation of haem kills the plasmodium.

Primaquine: It is active against all the hepatic forms of all species of Plasmodium. If uncomplicated infection is caused by *P. vivax* or *P. ovale*, it is important to treat with primaquine to prevent relapse. If species is initially unknown, primaquine treatment should be initiated. It binds to DNA and may disrupt the metabolic process of the parasite. Adult dose = 30 mg base PO, QID for 14 days. Pediatric dose = 0.5 mg base/kg PO, QID for 14 days.

Proguanil is a slow-acting erythrocytic schizonticide. The gametocyte is not allowed to develop in the mosquito. It is cycled in body to a triazine derivative which inhibits dihydrofolate reductase DHFRase in preference to the mammalian enzyme.

Pyrimethamine: It inhibits dihydrofolate reductase in the plasmodia that converts folic acid to folinic acid. It is mainly used for suppressive treatment of chloroquine resistant *P. falciparum* malaria.

Quinine: Levorotatory alkaloid from cinchona bark. It is erythrocytic schizonticide against all species of malaria, effectivity is lesser and is more toxic than chloroquine. The strains

resistant to mefloquine respond to quinine. It is efficacious in relieving acute attacks of falciparum malaria, may not prevent recrudescence. It binds to plasmodial DNA to prevent synthesis of protein. It is completely and rapidly absorbed orally. It is 70% bound to plasma protein acid glycoprotein.

Uses: Uncomplicated resistant falciparum malaria—7 days quinine 600 mg TDS oral + doxycycline 100 mg daily × 7 days + or/clindamycin 600 mg BD × 7 days.

For severe and complicated falciparum malaria—20 mg/kg diluted in 10 ml/kg 5% dextrose-saline infused IV over 4 hours followed by 10 mg/kg IV over 4 hours.

Adverse effects: Tinnitus, decreased auditory activity, headache, blurred vision, nausea and diarrhea (cinchonism), hypoglycemia, hypotension, hemolysis.

Artesunate and artemether are soluble derivatives of artemesinin, isolated from leaves of the Chinese herb, quinghaosu. The artemisinin derivatives have endoperoxide moiety causing antimalarial action by producing highly reactive free radicals which in turn, damage malarial proteins. The artemisinin derivatives are dihydroartemesinin used orally, artemether used orally or IM, artesenuate by oral, IM, rectal, IV route.

These agents are highly effective and exert very rapid action on the erythrocytic stage of plasmodia. They are active against the strains of *P. vivax*, chloroquine sensitive, chloroquine resistant, multidrug resistant strains of *P. falciparum.*

Riamet is fixed dose combination of artemether 20 mg and lumefantrine 120 mg, licensed for uncomplicated falciparum malaria. It is levorotatory alkaloid from cinchona bark. It is erythrocytic schizonticide for all species, less effective and more toxic than chloroquine.

Cerebral malaria: It is a disease caused by *P. falciparum* characterized by coma and asexual forms of the parasite in peripheral blood smears. Mortality is high and some patients sustain brain injury manifesting as long-term neurological sequelae. Quinine dihydrochloride, 600 mg diluted with 200–500 ml of 5% glucose solution infused IV over 4 hours. It is repeated every 8 hours till the patient is conscious. Oral therapy is then instituted to complete 7 days course. It is also used in:

- Hypoglycemia due to hyperinsulinemia—5% dextrose infusion
- Supportive treatment
- Night-time muscle cramps
- Diagnostic of myasthenia gravis
- As spermicidal in vaginal cream.

Artesunate by IV route is superior to IV quinine as it has higher efficacy, faster parasite clearance, better tolerated and safer.

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Chapter
38

Treatment of Tuberculosis

INTRODUCTION

Tuberculosis (TB) is a chronic granulomatous infectious disease and major health problem in developed and developing countries. Pulmonary TB is a bacterial infection of the lungs that can cause a range of symptoms including chest pain, breathlessness and severe coughing. Pulmonary TB can be life-threatening if a person does not receive treatment. People with active TB can spread the bacteria through air (Fig. 38.1).

It can affect other parts of the body like abdomen, glands, bones and nervous system. The typical symptoms of TB include a persistent cough that lasts more than 3 weeks and accompanied by phlegm, weight loss, high fever, tiredness and fatigue, loss of appetite, swellings in the neck.

- As per WHO data for 2012, in India alone 2.2 million people develop TB every year. Its control and treatment were under National Control Programme to provide free treatment to all. In 1997, a Revised National TB Control Programme was launched that also provides

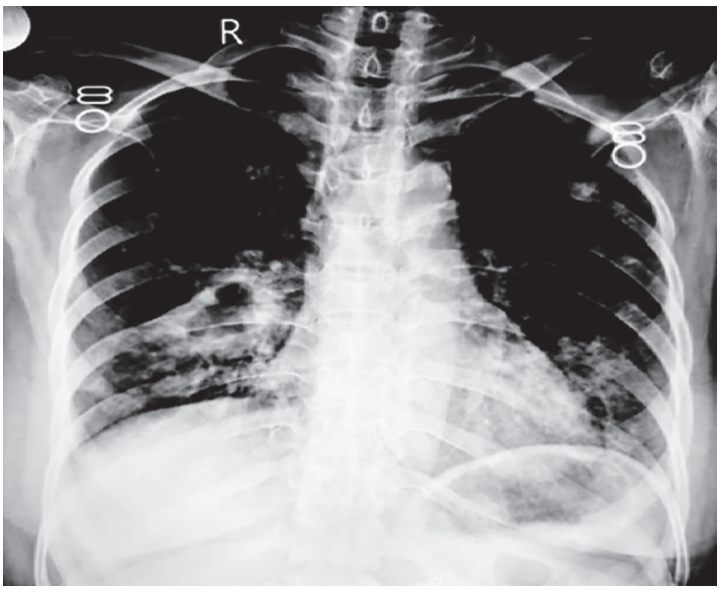

Fig. 38.1: Chest X-ray TB (*Image courtesy:* Chest and TB department, OPD, government Doon Medical College)

treatment guidelines. The drugs used for treatment of TB can broadly be divided into 2 major groups, the first- and second-line drugs.

- First-line drugs are highly efficacious, less toxic and used most commonly.
- Second-line drugs are less efficacious and more toxic as compared to first-line agents. They are expensive, inconvenient to use and used as reserve drugs only to treat multidrug resistant tuberculosis (MDR-TB).

FIRST-LINE DRUGS

- **INH:** Isoniazid, rifampicin, pyrazinamide, ethambutol
- **INH:** It exerts tuberculocidal action on rapidly multiplying bacteria and tuberculostatic effect on resting bacteria.
- It has good penetration into cells and kills the bacteria within the cells, i.e. both extracellularly and intracellularly including inside macrophages.
- The activity is similar in both the acidic and alkaline pH.
- The drug is highly selective for *Mycobacterium tuberculosis* (MTB). thus primarily inhibits the synthesis of mycolic acid and produces bactericidal action.
- INH metabolite forms adduct with NADP, causes inhibition of mycobacterial dihydrofolate reductase (DHFRase) and thus inhibits DNA synthesis.
- The dose is 5 mg/kg single dose
- Peripheral neuropathy is most common due to pyridoxine depletion as INH facilitates its excretion, more in slow acetylators. The symptoms are numbness, paresthesia of hands and feet and neuritis. Neuritis is more common in alcoholics, malnourished, diabetics .They must be given pyridoxine 10 mg OD as prophylaxis to prevent peripheral neuropathy. For treatment dose is 100 mg daily.
- **Rifampicin:** The members of this group are rifampicin, rifabutin, rifapentine and rifaximin. Rifampicin is a semi-synthetic derivative of rifamycin-B. It binds with β subunit of enzyme DNA dependent RNA polymerase and forms drug enzyme complex and thus inhibits chain formation in RNA synthesis. It exerts bactericidal effect on both the extracellular and intracellular mycobacteria and effect is more on persisters. It also affects semi-dormant bacilli but not dormant ones. It is the safest and least toxic drug, safest during pregnancy. Nausea, vomiting, fever, itching, flushing and rashes are common side effects.
- Mild transient increase in bilirubin and liver enzymes may occur.
- Reddish orange discoloration of skin, body fluids (sweat, saliva, tears), mucosal surface, urine and even soft contact lenses.
- **Pyrazinamide:** It inhibits mycolic acid synthesis but interacts with a different fatty acid synthetase encoding gene and exerts bactericidal effect. Its effect is optimum at acidic pH because MTB. exists in acidic phagosomes within the macrophage. It is highly effective against intracellular bacilli including inside macrophages and at site of inflammation.
- **Ethambutol:** It exerts selective tuberculostatic action. Peripheral neuropathy may precede the ocular toxicity. Optic neuritis is the most important side-effect, due to effect on amacrine and bipolar cells of retina and manifested as reduced visual acuity, loss of peripheral vision, central scotoma, inability to differentiate red from green colour. This may be reversible initially on stopping the drug but continuation of the drug may lead to permanent blindness.

- **Streptomycin:** It is tuberculocidal, penetrates TB cavities but acts only extracellularly. Its drawbacks are inability to enter cells, not very effective in acidic environment, does not penetrate blood–brain barrier (BBB) and there is development of resistance. Longer duration of action causes more chances of resistant bacteria, ototoxicity due to damage to auditory nerve, painful IM injection and nephrotoxicity.

SECOND-LINE DRUGS

1. **Ethionamide:** It also inhibits the synthesis of mycolic acid and exerts bacteriostatic action on both extracellular and intracellular MTB. It is widely distributed in various body tissues. Dose is 500 mg daily in 2 divided doses and increased gradually to 15–20 mg/kg. Ethionamide is used for multidrug resistant TB (MDR-TB). It is poorly tolerated. Nausea, vomiting, anorexia, gastric irritation postural hypotension, mental depression, sedation are common. Reversible hepatitis may occur. Neurological side effects are headache, dizziness, diplopia, blurred vision, paresthesia, tremors. Skin rashes, purpura, hypothyroidism, gynecomastia, impotence, menorrhagia, acne, alopecia and metallic taste may occur. Ethionamide inhibits the acetylation of INH.
2. **Paraaminosalicyclic acid (PAS):** It acts by inhibiting the synthesis of folic acid and exerts bacteriostatic action. The git side effects are nausea, anorexia, epigastric distress, burning and diarrhea. Hypersensitivity reaction such as skin rashes, fever, joint pain, granulocytopenia, goitre and hepatitis may occur. Dose is very high 10–12 g daily in 2 divided doses.
3. **Cycloserine:** It produces bactericidal or bacteriostatic effect depending on the concentration at the site of action. The adverse effects are of CNS. headache, sedation, tremors, vertigo, confusion, nervousness, dysarthria, suicidal tendency and convulsions. The dose is 500 mg in 2 divided doses. 150 mg pyridoxine per day reduces the neurotoxicity.
4. **Capreomycin:** The dose is 1 g IM route. 15–30 mg/kg daily. It is ototoxic causing cochlear toxicity leading to tinnitus, deafness and vestibular toxicity.
5. **Kanamycin and amikacin:** Both are cidal aminoglycosides effective against streptomycin resistant and MDR-TB. There is cross resistance between kanamycin and amikacin. Both have less vestibular toxicity than cochlear toxicity but similar nephrotoxicity. Dose—0.75–1g/day IM.
6. **Most of the fluoroquinolones (FQs)** are effective against MTB and atypical mycobacterium. The important ones are ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin and gemifloxacin. FQs are valuable drug for treatment of MDR-TB as well as atypical mycobacteria. Moxifloxacin causes rapid sputum conversion due to rapid killing of bacilli and suitable for treatment of MDR-TB and development of resistance is slow. Ofloxacin 800 mg OD, levofloxacin 1000 mg BD, moxifloxacin 400 mg OD.
7. **Clofazimine**—is antileprotic and can be used for MDR-TB when other agents fail. 200 mg daily dose.
8. **Linezolid**—is bacteriostatic antibiotic and recently indicated for resistant cases [MDR and extensively drug resistant (XDR) TB] 600 mg OD/BD. Its limitations are bone marrow depression, irreversible peripheral and optic neuropathy due to prolonged use.

9. **Bedaquiline** is recently approved by the United States Food and Drug Administration (USA FDA). It inhibits ATP synthetase, especially in MTB. It should be used with at least 3 other drugs active against patients TB isolate in treatment of MDR/XDR-TB. Nausea, joint pain, chest pain, headache are common side effects. It may prolong QT interval and cause potentially fatal cardiac arrythmias. Dose is 400 mg OD with food for first 2 weeks, from 3rd week to 24 weeks 200 mg 3 times per week. It has been recently approved in India for adults when there is no other effective regimen.

Goals of drug therapy: Multiple drugs are used to kill various subpopulation of bacteria, i.e. rapidly multiplying, slowly multiplying (including bacilli present inside macrophages), persisters and semidormant bacteria because one drug is not effective for all population of bacteria to prevent development of resistance, to reduce duration of therapy and to reduce drug toxicity.

Treatment regimens: All the regimens have 2 phases—initial intensive phase (to provide symptomatic relief, rapid bacilli killing, sputum conversion) with 4–5 drugs for 2–3 months, followed by continuation phase for 4–5 months with 2–3 drugs to cure condition, eradicate bacilli, prevent relapse. Drugs are administered daily or 3 times/week.

Regimen for new patients (category 1): Such patients should receive 4 drugs—HRZE initially that includes 3 tuberculocidal drugs in the intensive phase for 2 months followed by 2 drugs HR during continuation phase for 4 months, i.e. total 6 months. The intensive phase is extended by 1 month in cases remaining sputum smear + ve at the end of 2 months. Ethambutol is added in continuation phase in area with INH resistance.

Regimen for previously treated patient (category 2): Treatment using 5 drugs HRZES first-line for initial 2 months followed by 4 drugs for 1 month–HRZE because bacteria may be resistant to one or more first-line drugs. This is followed by next 5 months continuation phase with 3 drugs HRE, i.e. total 8 months.

Multidrug-resistant TB (MDR-TB): If bacilli is resistant to both H and R and any number of other first-line anti-TB drugs, considered multidrug-resistant TB. The disease progression is rapid and fatality may occur in short time of 2–4 months. Such cases are treated by second- line drugs for 24–27 months. The important causes of MDR-TB are HIV, diabetes mellitus, suppressed immunity due to leukemia or drugs, i.e. corticosteroids.

Often 5–6 drugs are used of which efficacy of at least 4 drugs is definite.

Drugs used in **intensive phase** (6–9 months)—kanamycin, ofloxacin, ethionamide, cycloserine, pyrazinamide, ethambutol.

Drugs used in **continuation phase** (18 months)—ofloxacin, ethionamide, cycloserine, ethambutol. All the patients are given supplementary 100 mg pyridoxine/day. Minimum intensive phase is 6 months which is extended each month to a maximum of 9 months on basis of positive sputum culture report at the end of 4th, 5th and 6th month, respectively. The regimen may be individualized on basis of drug sensitivity test (DST) results, tolerance and toxic effects of drugs in an individual patient.

Extensively drug-resistant TB (XDR-TB): The cases who have developed resistance to 4 most highly effective tuberculocidal drugs such as H + R + all FQs + one injectable (Km, Am, Cm) + resistant to any number of other drugs. The cases showing failure to MDR-TB regimen may be considered XDR-TB. These cases are difficult to treat and carry high mortality.

Treatment for Patients with XDR-TB

- Use pyrazinamide and any other group 1 that may be effective.
- Use an injectable agent—group 2—streptomycin, kanamycin, amikacin, capreomycin, if which strain is susceptible for 12 months.
- Use all group 4 agents (oral bacteriostatic second-line drugs—ethionamide, cycloserine, linezolid, clofazimine) that have not been used extensively in a previous regimen.
- Use a higher generation fluoroquinolone—group 3-moxifloxacin or gatifloxacin.
- Add 2 or more group 5 drugs. Add bedaquiline or delamanid.
- Consider high dose isoniazid treatment if low level resistance or absence of kat G gene.
- Consider adjuvant surgery if there is localized disease.
- Rigorous respiratory infection control measures done.
- The duration of treatment is 18–20 months. Dose of linezolid has to be tapered to 300 mg after initial 6–8 months of treatment. Bedaquiline has to be given for 6 months.

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Chapter
39

Treatment of Viral Illness

VIRUS STRUCTURE

Viruses are small infective agents 20–30 nm that are incapable of reproduction outside their host cells. The free-living virus particle is termed virion, and consists of segments of nucleic acid (DNA or RNA) enclosed in a protein coat comprised of symmetrical repeating structural units called a capsid. The viral coat together with the nucleic acid core is called the nucleocapsid. Some viruses have a further external lipoprotein envelope. It may be decorated with antigenic viral glycoproteins or phospholipids acquired from its host (Fig. 39.1).

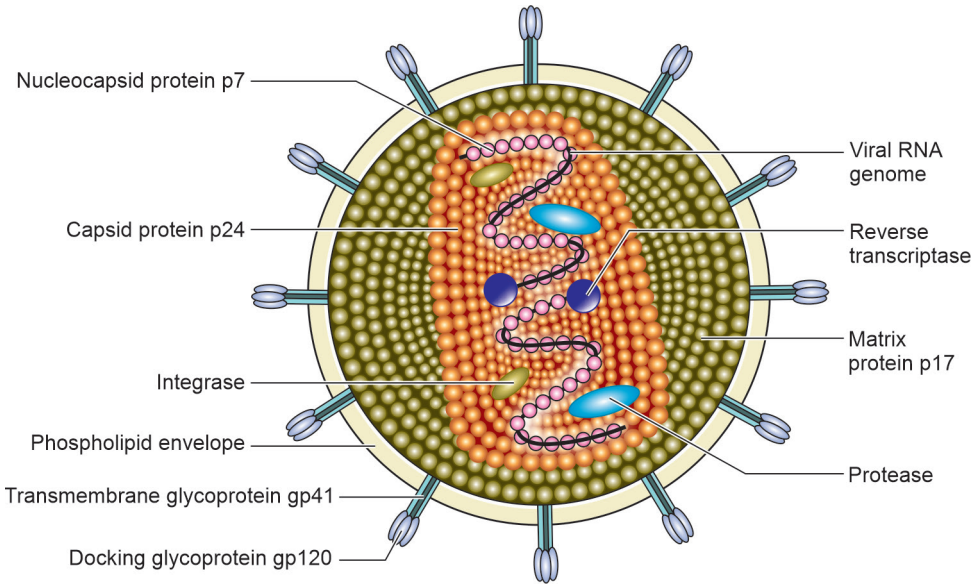

Fig. 39.1: Virus structure

Viral function and life history: As viruses have no metabolic machinery of their own, they have to attach to and penetrate a living host cell and utilize the hosts metabolic machinery to replicate. The first step in this process is facilitated by polypeptide binding sites on the envelope or capsid which interact with receptors on the host cell. Following attachment, the receptor virus complex enters the cell during which time the virus coat may be removed by host cell enzymes.

Replication of DNA viruses: Viral DNA enters the host cell nucleus, where transcription into mRNA occurs catalysed by the host cell RNA polymerase. Translation of mRNA into virus specific proteins then take place. Some of these proteins are enzymes that then synthesise more viral DNA, as well as structural proteins comprising the viral coat and envelope. After assembly of coat proteins around the viral DNA, complete virions are released by budding or after host-cell lysis (Fig. 39.2).

Replication of RNA virus: Enzymes within the virion synthesise its mRNA from the viral RNA template or sometimes the viral RNA serves as its own mRNA. This is translated by the host cell into various enzymes, including RNA polymerase and also into structural proteins of the virion. Assembly and release of virions occurs. The host cell nucleus is usually not involved in replication of RNA viruses, although some, e.g. orthomyxoviruses replicate exclusively within the host nuclear compartment.

Virus ploys to circumvent host defences: Viruses can inhibit the synthesis or action of cytokines, such as interferon 1, TNF-α and the antiviral interferons that normally coordinate the innate and adaptive immunity Some pox viruses express proteins that mimic, the extracellular ligand binding domains of cytokine receptors. These pseudoreceptors bind cytokines, e.g. preventing them from reaching their natural receptors on cells of the immune system. Other viruses that can interfere cytokine signaling include CMV, EBV, herpes virus and adenovirus.

RNA retroviruses, e.g. HIV, T-cell leukemia virus contain an enzyme reverse transcriptase, which makes copy of the viral RNA. This DNA copy is integrated into the host cell genome and directs the generation of new virus particles.

Virus–host interactions: They may cause different effects from no apparent cellular damage to rapid cell destruction.

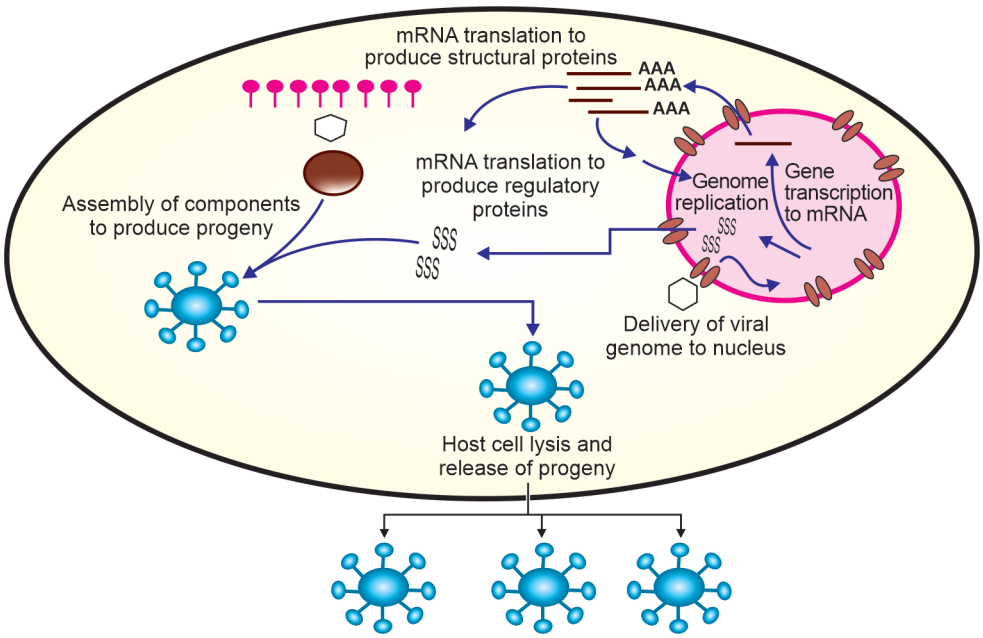

Fig. 39.2: Life cycle of virus replication

Some viruses cause cell death, e.g. poliovirus. Others may cause cellular proliferation or malignant transformation (oncogenic viruses). In some instances, virus remains as latent infections (herpes simplex) whereas others produce some morphological changes in cells to form inclusion bodies, e.g. rabies virus.

The variola virus causes small pox.

Herpes viruses consist of a number of DNA viruses, characterized by their ability to establish lifelong latent infections which enable them to undergo periodic reactivation.

Herpes simplex virus (HSV1): Causes acute gingivostomatitis, herpes labialis, kerato-conjunctivitis, encephalitis, dendritic keratitis. HSV2 causes genital herpes, neonatal herpes, aseptic meningitis.

Varicella zoster virus: Causes varicella (chickenpox) and herpes zoster. Chickenpox follows primary infection whereas herpes zoster is a reactivation of the latent virus when immunity falls.

Epstein-Barr virus (EBV): Has affinity for lymphoid tissue. The virus affects the B-lymphocytes. The clinical manifes tations are Infectious mononucleosis, infections in immunocompromised hosts, Burkiit's lymphoma, tumor of the jaw, nasopharyngeal carcinoma, B-cell lymphoma

Human herpes virus 8: Has been associated in causation of Kaposi sarcoma, which is the commonest tumor in HIV-infected individuals.

Picornaviruses—enteroviruses cause poliomyelitis.

Rhinoviruses—are causative agents for common cold.

Orthomyxoviruses—are spherical or filamentous enveloped viruses with single-stranded and segmented RNA genome. They cause influenza—an acute respiratory disease with prominent systemic symptoms.

Paramyxoviruses—can cause respiratory infections in children and often in adults. They cause severe respiratory tract disease such as laryngo-trachea-bronchitis or croup. They can cause mumps, measles, bronchiolitis and pneumonitis.

Respiratory syncytial virus (RSV)—causes common cold and infections of respiratory tract.

Arboviruses

a. **Chikungunya virus** transmitted by *Aedes aegypti.*
b. **Flavivirus** causes Japanese encephalitis.
c. **Dengue** caused by dengue virus.
d. **Rhabdoviruses**—bullet or rod-shaped with single-stranded RNA genome, cause rabies
Hepatitis virus—causes hepatitis of 6 types—A, B, C, D, E, G. Hepatitis is a systemic disease with primary inflammation in the liver. Hepatitis B is a DNA virus while others contain RNA genome.

DRUGS CLASSIFICATION

1. **Antiherpes:**
   a. Mainly for herpes virus and VZV, e.g. acyclovir, valacyclovir, penciclovir, famciclovir, foscarnet, vidarabine, idoxuridine
   b. Mainly for CMV—cytomegalovirus (Cytosine analogue–cidofovir)
   Guanine analogue, e.g. ganciclovir
   Others—fomivirsen, foscarnet

2. **Antiinfluenza drugs:** Amantadine, rimantadine, zanamivir, oseltamivir, peramivir and ribavirin.
3. **Antihepatitis drugs: (**Hepatitis B), e.g. lamivudine, adefovir, interferon, entecavir, tenofovir.
4. **Antiretroviral drugs**
5. **Other drugs—**interferons, globulins, monoclonal antibodies, e.g. palivizumab.

Acyclovir: It is guanine derivative, a prodrug having 200 times more affinity for viral HSV thymidine kinase than human thymidine kinase. Its spectrum is limited to herpes group of viruses. Acyclovir is phosphorylated by virus specific thymidine kinase to acyclovir monophosphate which is later converted into acyclovir triphosphate by host cell enzymes. The concentration of acyclovir triphosphate achieved in HSV-infected cells is up to 100 times more as compared to uninfected cells. It gets incorporated into viral DNA and terminates DNA strand. Terminated DNA strand containing acyclovir binds and inhibits viral DNA polymerase irreversibly.

Clinical Uses

a. **Mucocutaneous herpes:** It is due to HSV1 localized to lips and gums. Acyclovir may be used orally for about 10 days. It is also used orally for treatment of gingivostomatitis, pharyngitis, herpes proctitis in immunocompromised patients 15 mg/kg/day for 7 days.
b. **Keratoconjunctivitis:** For HSV infection, topically acyclovir is effective because of good corneal penetration and used with oral medication. Eye ointment is used 5 times a day and continued for a few days after healing.
c. It is used by IV route in all the severe cases of HSV infection, herpes encephalitis, neonatal HSV infection, disseminated mucocutaneous herpes.
d. **Varicella and zoster infection:** It reduces the cutaneous and visceral spread. Higher doses are used.
   i. **Varicella (chickenpox):** The dose is 800 mg BD, used IV 20 mg/kg 8 hrly in neonates, in immunocompromised patients, 10 mg/kg IV in pneumonia as infusion over 1 hour and repeat 8 hourly for 7–10 days.
   ii. **Herpes zoster:** Due to reactivation of virus lying dormant in dorsal root ganglia. Acyclovir is used in severe cases of immunocompromised patients 800 mg 5 times a day oral, reduces the symptoms and healing of ulcer is facilitated. Used topically as 5% ointment. In severe cases 5–10 mg/kg as IV infusion over 1 hour and repeated 8 hourly for 7 days.

Prophylactic use in patients receiving immunosuppressants: It is used for prevention of reactivation of HSV infection due to immunosuppressants used in patients undergoing organ transplantation 200 mg 8 hourly or IV 5 mg/kg 8 hourly.

It is well-tolerated orally. The side effects are nausea, diarrhea, headache and malaise. IV use may cause vomiting, rashes, sweating. The continuous IV infusion may cause renal dysfunction, reversible. Reversible neurotoxicity may also result in form of tremors, delirium, disorientation, convulsions. The incidence is reduced if adequate hydration is maintained and rate of infusion is slow. Topical use may cause stinging and burning sensation.

Valacyclovir: L-allyl ester prodrug of acyclovir. It is actively transported to intestine by peptide transporter and thus increases oral BA. On oral administration, it is rapidly and

completely converted to acyclovir during 1st pass in the intestine and liver by enzymatic hydrolysis. The plasma concentration. achieved is 4 times higher than acyclovir and thus better therapeutic effect. The uses are in genital herpes, herpes zoster and prevention of CMV disease after organ transplantation. The side effects are similar to acyclovir However when used in toxic doses (8 g/day) as in AIDs patients, the incidence of GIT side effects, thrombotic thrombocytopenic purpura and hemolytic uremic symptoms and neurological side effects such as confusion and hallucinations in patients undergoing organ transplantation is increased. It is more efficacious than acyclovir and reduces duration of pain due to herpes zoster, reduces frequency of postherpetic neuralgia and reduces sexual transmission. The dose for herpes zoster is 1 g TDS for 7 days.

Famciclovir: Cross resistance is observed with acyclovir and famciclovir. It is used as an alternative to acyclovir for both HSV and VZV infections. 500 mg TDS × 7 days.

Cidofovir: Having in vitro activity against many viruses such as CMV, HSV1, HSV2, VZV, HHC_6, HHV 8, adenovirus, poxvirus, polyoma virus and papilloma viruses. It inhibits viral DNA polymerase after activation to diphosphate by cellular enzymes. Its plasma t1/2 life is 2–3 hours but its metabolite cidofovir diphosphate has very long duration. (1–3 days). It is mainly used for CMV retinitis (5 mg/kg IV every week followed by same dose every 2 weeks). Probenecid should be used with cidofovir as the peak conc achieved is higher because probenecid blocks its secretion as it is excreted unchanged by active renal tubular secretion.

Ganciclovir: Guanine analog chemically related to acyclovir with similar mechanism of action. It is active against HSV, VZV, EBV, CMV. Its activity against CMV is up to 100 times more than acyclovir due to much higher conc of ganciclovir triphosphate (active drug) in CMV infected cells. Its oral BA is low due to poor absorption. The CSF conc is 50% of plasma concentration It is readily removed by hemodialysis. Its major portion is excreted unchanged in urine. Its plasma t1/2 life is about 2–4 hours but effect persists for 24 hours because intracellular t1/2 of its triphosphate is about 24 hours.

It is reserve drug of choice for severe CMV infection (retinitis, pneumonia, colitis) in AIDs patients as prophylactic for patients of organ transplantation. 5 mg/kg BD for 1–3 weeks, then 5 mg/kg OD for prophylaxis and treatment of CMV infections in immunocompromised. It is more toxic than acyclovir and serious systemic toxicities are bone marrow depression and neuropsychiatric disorder (headache, convulsions, behavioral change), also minor side effects-fever, rash, vomiting.

Foscarnet: Acts by inhibiting viral DNA polymerase, RNA polymerase, HIV reverse transcriptase without activation by phosphorylation. It is indicated for CMV retinitis in AIDs patients resistant to ganciclovir. It is equally efficacious, used as IV infusion.

Fomivirsen: It is oligonucleotide that acts by antisense mechanism to inhibit the CMV. It is used intravitreally for CMV retinitis in AIDs patients resistant to ganciclovir, cidofovir and foscarnet.

Antiinfluenza drugs: Influenza is of 2 types, type A type B. Influenza type B usually occurs in humans while influenza A affects other species. There are many strains of influenza virus A, B, C species in which originated. They are classified on basis of surface proteins into 16 types and 9 subtypes, e.g. H_1N_1. H means type of haemagglutinin present and N means type of neuraminidase present. The H_5N_1 caused birdflu and also caused severe disease in humans

and proved fatal in southeast Asia. In recent years infection with H_1N_1 was responsible for swineflu in humans. The drugs used for treatment are:

1. **Amantadine:** It is tricyclic amine and acts by 2 mechanisms. At early step it inhibits the uncoating of viral RNA of influenza A within host cells and late step it inhibits viral assembly during replication. It is mainly used for prophylaxis and treatment of influenza A_2 and also effective against rubella. The dose is 100 mg BD.
2. **Rimantadine:** It has higher oral bioavailability with similar clinical uses. It is excreted in urine after extensive metabolism by hydroxylation and glucuronidation. So, dose should be reduced in hepatic disease. The dose should also be reduced in elderly and in patients with renal disease but GIT intolerance is more. It is also used for treatment of Parkinsonism. 100 mg BD.
3. **Oseltamivir:** It is a prodrug and used orally. It acts by inhibiting neuraminidase enzyme and so inhibits viral replication and release of progeny virus into uninfected cells. It is active against influenza A and B including strains resistant to amantadine. Resistance develops due to mutation in enzyme neuraminidase. It is activated in the gut and liver by esterase to active form oseltamivir carboxylate. Dose reduction is required in poor renal function. It is DOC for treatment (75 mg BD) and prophylaxis (75 mg OD) of influenza A_2 for 5 days. Also used in bird flu (H_5N_1) and swine flu (H_1N_1) in the same dose.
4. **Zanamivir:** Its mechanism, efficacy and clinical uses are similar to oseltamivir and equally effective. It is effective for influenza A and B including amantadine and oseltamivir resistant strains. The treatment should be started within 1–2 days and this reduces the severity, duration and respiratory complications of disease in both adults and children. It has poor oral BA, poor plasma protein binding and excreted rapidly unchanged. It is used as inhalation through IV specific inhaler, 10 mg BD for treatment and OD for prophylaxis for 5 days. It may precipitate bronchospasm in asthmatics.

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Chapter
40

Treatment of AIDS (Acquired Immunodeficiency Syndrome)

It is acquired profound immunodeficiency marked by vigorous viral replication, CD_4 lymphocyte depletion. It was first reported in 1981 in US in cases of *Pneumocystis carinii* pneumonia and Kaposi's sarcoma in homosexual men.

ETIOLOGICAL AGENTS

HIV was formerly called lymphadenopathy-associated virus (LAV), HTLVIII and ARV (AIDS-associated retrovirus). The virus shows tropism for CD_4 molecule. CD_4 T cells are important targets of viral infection.

- Family: Retrovirus
- Subfamily: Lentivirus

  Human retrovirus is divided into 2 categories:
  - Transforming retrovirus—HTLV I and III
  - Cytopathic retrovirus—HIV 1 and 2

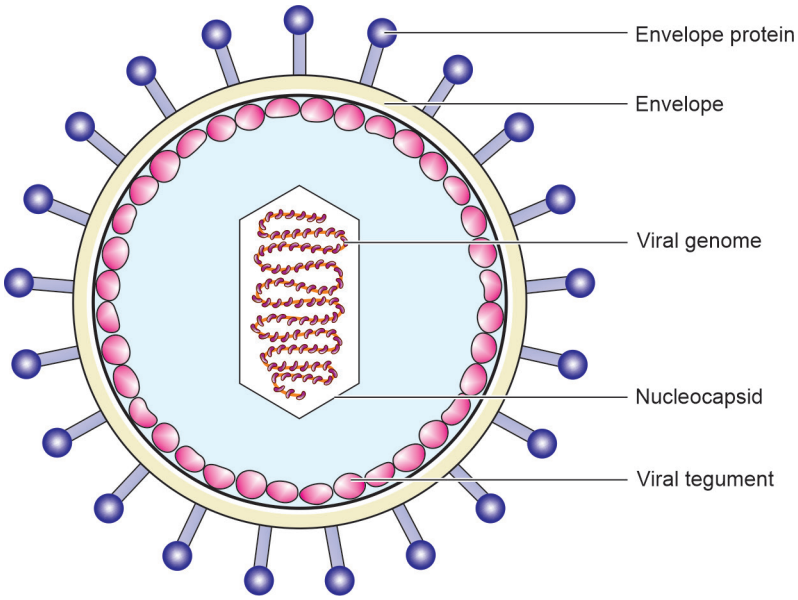

Fig. 40.1: HIV structure

Majority of cases of AIDS are caused by HIV1. HIV2 is prevalent cause of AIDS in West Africa.

Transmission of HIV: Transmitted by homosexual and heterosexual contact. Half the cases in US are among homosexuals. In developing countries, it is transmitted mostly by heterosexual method. The transmission risk is higher with anal than with vaginal intercourse and greater for penetrative sex.

The virus is seen in seminal fluids within mononuclear cells and cell-line state. It is also seen in cervical smears and vaginal fluid.

Transmissions is by:

1. Blood and blood products:
2. Sharing paraphernalia
3. Injection drug users
4. Occupational transmission of HIV to healthcare workers, risk is 0.3%.
5. From infected mother to her fetus through placenta or to her infant after delivery, risk is approximately 25%.
6. Transmitted through other body fluids, saliva

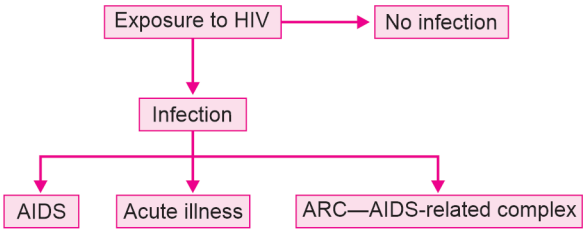

Fig. 40.2: Natural history of HIV infection

Pathophysiology: During the course of HIV disease, there is gradual lowering in CD_4 cells count in peripheral blood. HIV infection causes abnormality of immune function resulting in deficient cell-mediated immunity which protects against intracellular parasites, e.g. virus, protozoa and mycobacteria. Failure of appropriate antibody response results in infection with capsulated bacteria. HIV also affects CNS system due to migration of HIV-infected monocytes to the brain. HIV infection is a result of immune system failure resulting in opportunistic infections and secondary neoplasms.

Natural history of HIV infection: HIV infection is followed by seroconversion following a latent period of 3 weeks. In one-third individuals, it is characterized by clinical illness for about 2 weeks after which HIV appears in blood. Symptoms of illness include fever, malaise, headache, arthralgia, macular papular rash and tender lymphadenopathy (Fig. 40.2).

Serconversion → Subclinical Immunological Abnormalities—Increasingly Severe Clinical Immunological Abnormalities

Diagnosis: HIV infection is confirmed by demonstrating the presence of antibodies to HIV in the patient's serum. Confirmation of diagnosis is by more precise Western Blot test which also detects the presence of anti-HIV antibodies. Following infection, seroconversion may not occur as long as 3 months or longer. The patient presents with wasting, oral candidiasis, oral hairy leukoplakia, splenomegaly and perianal herpes.

SECONDARY INFECTIONS AND NEOPLASMS IN THE PATIENTS WITH HIV INFECTION

Protozoal and helminthic infections (parasitic infections)

- Cryptosporidiosis
- Pneumocystosis infections

- Toxoplasmosis
- Strongyloidosis

Fungal infections
- Candidiasis
- Cryptococcosis
- Coccidiomycosis
- Histoplasmosis
- Other opportunistic mycosis

Bacterial infections
- Mycobacteriosis
- Nocardiosis
- *Salmonella* infections

Viral infections
- Cytomegalovirus
- Herpes simplex virus
- Varicela zoster virus

Malignant neoplasms
- Burkitt's lymphoma
- Kaposi's sarcoma

Classification of AIDS

ABSOLUTE CD_4 (/mm^3) count—Group A = 500/mm^3, Group B = 200–499/mm^3, Group C < 200/mm^3.

Group A: Acute HIV infection, asymptomatic phase or persistent generalized lymphadenopathy.

Group B: Symptomatic, anything except those in Group C (constitutional symptoms, oral candidiasis, peripheral neuropathy, ITP).

Group C:
- Disseminated clinical CMV infection
- Chronic mucocutaneous herpes simplex infection
- Progressive multifocal leucoencephalopathy
- Extrapulmonary or pulmonary TB
- *Pneumocystis carinii* pneumonia
- Disseminated *Mycobacterium avium* intracellulare
- Candidiasis of esophagus, bronchi or pulmonary
- Chronic cryptosporidiosis
- Toxoplasmosis of brain
- Disseminated histoplasmosis
- Cryptococcosis
- Strongyloidiasis
- Secondary neoplasms—Kaposi's sarcoma
- Primary lymphoma of brain
- Non-Hodgkin's lymphoma

INITIAL EVALUATION OF THE PATIENT

- History and physical examination
- Routine chemistry and hematology
- CD_4T lymphocyte count
- Two plasma HIV-RNA levels
- VDRL Test
- Anti-toxoplasma antibody titer
- PPD skin test (purified protein derivative)
- Mini mental status examination
- Serologies for hepatitis A and B
- Immunisation with hepatitis A and B if seronegative
- Counselling regarding natural history and transmission
- Help contacting others who might be infected

PRINCIPLES OF THERAPY OF HIV INFECTION

HIV replication is ongoing, destroys the immune system and causes progression to AIDS.

The magnitude of HIV replication and CD4 cell destruction are indicated by plasma HIV RNA levels.

CD4 Tcell counts are indicative of present competence of the immune system.

The rate at which disease progresses differs among individuals, and treatment is individualized based upon the levels of plasma HIV-RNA and CD4 T cell counts.

The goal of therapy is maximal suppression of viral replication.

The initiation of combinations of effective anti-HIV drugs with which the patient has not been previously treated. and that are not cross resistant with antiretrovirals that patient has already received, is the most effective therapeutic strategy.

The combination regimens should be used in accordance with optimum schedules and dosages.

As the number of available drugs is limited, any decisions on antiretroviral therapy (ART) have a long-term impact on future options for the patient.

Women should receive optimum antiretroviral therapy irrespective of pregnancy status. The same principles apply to children and adults.

Compliance is necessary for ensuring maximal effect for a given regimen. The simpler the regimen, the easier it is for the patient to be compliant.

DRUG CLASSIFICATION AND MECHANISM OF ACTION AND IMPORTANT POINTS

HIV replication suppression is an important task in prolonging and improving the quality of life in patients with HIV.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

NRTIs act by competitive inhibition of HIV1 reverse transcriptase as they act at an early step of viral replication. They prevent acute infection of susceptible cells. To become active, these drugs must be phosphorylated by host cell enzymes in the cytoplasm to the triphosphate form. Their side effects include lactic acidosis, hepatomegaly with steatosis.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

NNRIs bind directly to a site on the viral transcriptase that is near to but distinct from the binding site of NRIs. They neither compete with nucleoside triphosphates nor require phoshorylation to be active. They have activity against HIV1 and HIV2. The rapid emergence of resistance prohibits monotherapy with any of the NNRIs during treatment of HIV infection. There is no cross resistance between NRIs and the NNRIs or protease inhibitors. All compounds of this class are metabolised by CYTP 450 system and are prone to drug interactions. Their side effects are headache, hepatotoxicity and skin rash especially. with delavirdine.

PROTEASE INHIBITORS (PIs)

The viral protease is essential for viral infectivity, cleaves the viral polyprotein into active viral enzymes and structural proteins. Monotherapy lowers plasma HIV RNA approx. 100–1000 fold within 4–12 weeks. Most HIV protease inhibitors undergo oxidative metabolism by CYTP3A4 and additional CYTP isoforms. Toxicities—nausea, vomiting, diarrhea and paresthesias. Long-term use is associated with fat re-distribution like buffalo hump, breast enlargement and subcutaneous lipomas. All protease inhibitors are both substrates and inhibitors of CYTP isoforms.

Drugs–NRTIs

Zidovudine—is used in treatment of HIV infection when antiretroviral therapy is indicated. The dose is 2000 mg 8 hourly or 300 mg BD. The toxicity includes anemia, granulocytopenia, and lactic acidosis, hepatomegaly with steatosis, headache, and nausea.

Didanosine—is used for treatment of HIV infection when antiretroviral therapy is warranted. The dose required is 2 tablets to achieve adequate buffering of stomach acid. The toxic reactions are pancreatitis, peripheral neuropathy, abnormality of liver function tests. Dose—400 mg/day.

Zalcitabine—is used in combination with other antiretrovirals for the treatment of HIV infection. The dose is 0.75 mg TID. The toxic effects are peripheral neuropathy, pancreatitis, lactic acidosis, hepatomegaly with steatosis.

Stavudine—is used in treatment of infected patients who have received prolonged treatment with Zidovudine therapy, 30 mg BD.

Lamivudine—is used in combination with other antiretrovirals for the treatment of HIV infection. The dose is 150 mg BD.

Abacavir—is used for treatment of HIV in combination with other antiretrovirals. The dose is 300 mg BD. The toxic reactions are hypersensitivity reaction, fever, rash, nausea, malaise.

NNRTIs

Delaviridine—is used in combination with other antiretrovirals. The dose is 400 mg TID. The side effects are skin rash, abnormalities in liver function tests.

Nevirapine—is used in combination with nucleoside analogues for treatment of progressive HIV infection. The dose is 200 mg/day × 14 days, then 200 mg BD.

Efavirenz—is used for treatment of HIV in combination with other antiretrovirals. The dose is 60 mg q 8 hourly. The toxic effects are rash, headache, elevated liver function tests.

Saquinavir—is used in combination with other antiretrovirals. The dose is 600 mg q 8 hourly. The side-effects are diarrhea, nausea, headache, hyperglycemia, fat redistribution, and lipid abnormalities.

Ritonavir—is used in combination with nucleoside analogues for treatment of HIV infection. The dose is 100 mg BD. The toxic effects are nausea, abdominal pain, hyperglycemia, fat redistribution, and lipid abnormalities. Ritonavir is potent CYP3A4 inhibitor.

Treatment

Use of potent combination antiretroviral therapy and prophylactic intervention plays a vital role in providing each patient with productive life the, despite the presence of HIV infection.

COMBINATION ANTIRETROVIRAL TREATMENT STRATEGY

Conservative approach: Individuals with CD_4 counts between 200 and 500/mm^3 should receive zidovudine only if there are symptoms. For patients with CD_4 count below 200/mm or with AIDS, zidovudine is generally recommended. Later switching to alternative therapy may be beneficial.

Then treatment is done with

- Didanosine monotherapy
- Zidovudine + Didanosine
- Zidovudine + Lamivudine

The chosen regimen is used until the disease demonstrated progression with CD_4 T cell count >200/µl. Therapy is then changed. The most prudent choice of treatment—two nucleosides and a protease inhibitor.

Aggressive approach: Combination therapy is started from the time of diagnosis of HlV infection. Highly aggressive anti-retroviral therapy (HAART) should be started to suppress plasma viral load to undetectable levels <50 copies of HIV-RNA/ml. Therapy with three anti-retrovirals zidovudine + lamivudine + indinavir is done. Patient is monitored for changes in CD4 T cell count and plasma levels of HIV-RNA. 25% decrease in CD4 count indicates for a change in therapy.

Current therapy: Falls between two options influenced by facts:

- Median time from infection to clinical disease is 10 years. For symptomatic patient with stable CD_4 T cell count >500/µl and plasma viremia <20,000 copies/ml, no treatment but repeat evaluations should be done every 6 months. Beyond this, treatment started with two nucleosides plus protease inhibitor.
- The regimen should be changed if plasma HIV level rose above baseline by 0.5 log or CD_4 + T cell count falls by >25 % due to treatment failure. A regimen with two new drugs is provided. In case of drug toxicity—substitution with one drug is done.

ART Combination

The most combination antiretroviral regimens in patients generally consist of:

- Two NRTIs plus one NNRTI, or
- Two NRTIs plus a PI (with or without ritonavir boosting).

- 3 NRTIs
- Stopping of therapy during an acute opportunistic infection should not be done except in case of intolerance, interactions or toxicity.

INDICATIONS FOR INITIATION OF ANTIRETROVIRAL THERAPY

1. Acute infection syndrome.
2. Chronic infection
   a. Symptomatic disease
   b. Asymptomatic diseases—A CD_4 T cell count <500/µl or decreasing or HIV-RNA >20,000 copies/ml or increasing.
3. Postexposure prophylaxis

INDICATIONS FOR CHANGING ANTIRETROVIRAL THERAPY

Following the initiation of therapy, less than a 1-log drop in change in plasma HIV-RNA by 4 weeks.

- Plasma viral load above 5000 copies/ml.
- Persistent CD_4 levels below 100 cells/mm^3
- Clinical worsening-changes in respiratory rate, oxygen saturation, blood pressure, heart rate, temperature and consciousness.
- Preventing short-term or long-term adverse effects.
- The first dose of PEP should be administered immediately within 2 hours and preferably within 72 hours of exposure.
- Healthcare personal should be instructed about the safety of the PEP drugs
- Duration of PEP is 28 days, regardless of PEP regimen.

T-11020/36/2005/NACO/(ART) Part I Government of India
Ministry of Health and Family Welfare National AIDS Control Organisation

Table 40.1: Revised ARV regimens for postexposure prophylaxis (PEP) for HIV infection

Exposed person	*Preferred regimen for PEP (drugs and dosages)*	*Alternate regimen (if the preferred regimen is not avilable or contraindicated)*
Adolescents and adults (>10 years of age and >30 kg weight)	**Tenofovir (300 mg) + Lamivudine (300 mg) + Dolutegravir (50 mg)** (FDC—one talet OD)	**Tenofovir (300 mg) + Lamivudine (300 mg)** (FDC—one talet OD) + **Lopinavir** (200 mg)/Ritonavir **(500 mg) two tablets BD)** or **Tenofovir (300 mg) + Lamivdine (300 mg) + Efavirenz (600 mg)**
Children (>6 years and >20 kg weight)	Zidovudine + Lamivudine (Lopinavir/ritonavir (dose as per weight band))	If Hb <9 g/dl: **Abacavir + Lamivudine** (dosage as per weight band) + **Dolutegravir** (50 mg) (1 tablet OD)
Children (<6 years old and or <20 kg weight)	Zidovudine + Lamivudine + Opinavir/Ritonavir (dosage as per weight band)	If Hb <9 g/dl: **Abacavir + Lamivudine** + **Lopinavir/Ritonavir** (dosage as per weight band)

Table 40.2: Guidance for first-line regimen in PLHIV (adults and adolescents)	
PLHIV group	***Regimen***
Preferred first-line regimen for ART intiation in PLHIV with age 10 years and weight >30 kg	Tencifovir (300 mg) + Lamivudine (300 mg) + Dolutegravir (50 mg) in an FDC—one tablet once daily (at bedtime or any fixed time every day as per patient's convenience)
PLHIV with age >10 years and weight <30 kg	Abacavir + Lamivudine + DC (as per body weight) + Dolutegravir (DTG) (50 mg)—one daily at same time as AL
Female in reproductive age group who do not want to use TLD	Tencofovir (300 mg) + Lamivudine (300 mg) + Efavirenz (600 mg) If efavirenz is contraindicated (HIV2/HIV1 and 2/prior NNRTI exposure) than tencolfovir + lamivudine + lopinavir + ritonavir (TL—IOD, LPV 200/50—2BD)
PLHIV or rifampic in containing ATT regimen	Additional dose of DTG to be provided along with recommended DTG-based regimen (12 hours after taking their regular dose) for the duration of TB treatment

PLHIV—people living with HIV

Table 40.3: Guidance for first-line regimen for ART initiation in children	
Weight and age	***Recommednded regimen***
Weight less than 20 kg or age below 6 years	Tab abacavir +Tab lamivudine—FDC (as per body weight) + Tab lopinavir/ritonavir (as per body weight) It coinfected with TB and on concomitant rifampicin containing ATT superboosting with ritonavir
Weight between 20.3 kg and age between 6–10 years	Tab abacavir + Tab lamivudine—FDC (as per body weight) + Tab dolutegravir 50 mg If coinfected with TB and on concomitant rifampicin containing ATT. Additional dose of tab dolutegravir 50 mg after 12 hours for the duration of TB treatment
Weight above 30 kg and age above 10 years	Tab tenofovir (300 mg) + Tab lamivudine (300 mg). Tab dolutegravir 50 mg—FDC one tablet ones daily (at bedtime or any fixed time every day as per patient's convenience) If coinfected with TB and on concomitant rifampicin containing ATT. Additional dose of tab dolutegravir 50 mg after 12 hours for the duration of TB treatment.

COMBINATIONS

Combivir: Zidovudine + Lamivudine

Trizivir: Zidovudine + Lamivudine + Abacavir

Lopinavir: Lopinavir + Ritonavir

OPPORTUNISTIC INFECTIONS

These are late complications of HIV infection occurring in patients with CD_4+T cells <200 microlitre.

Table 40.4: Revised guidance for second-line ART regimen for PLHIV failing on first-line ART

First-line ART regimen		*Second line ART regimen*
Zidovudine containing	NNRTI/PI-based first-line	Tenofovir (300 mg) + Lamivudine (300 mg) + Dolotegravir (50 mg)—FDC It patient has contraindication to TDE Abacavir (600 mg)—Lamivudine (300 mg)— + Dolutegravir (50 mg)—FDC If HB ≥9 g/dl
Tenofovir/Abacavir containing	NNRTI-based first-line	Zidovudrine 300 mg + Lamivudine 150 mg FDC (BD) + Dolutegravir 50 mg (OD) If HB <9 g% Atazanavir + 300 mg Lopinavir/ritonavir (200/50 mg, 2 BD) + Dolutegravir (50 mg) (OD) + existing NRTI backbone*
	PI-based first-line	Zidovudine 300 mg + Lamivudine 150 mg FDC (BD) + Dolutegravir 50 mg (OD) If Hb ≥9 g/dl Darunavir 600 mg [BD] + Ritonavir If Hb <9 g/dl 100 mg (BD) + Dolutegravir 50 mg [OD] + existing NRTI backbone*
Multi-NRTI exposed	NNRTI-based first-line	Lopinavir/ritonavir (200/50 mg, 2BD) + Dolutegravir (50 mg) (OD) + existing NRTI backbone*
Any PLHIV co-infected with TB receives BD dose of DTG unitil the patient completes ATT and thereafter OD dose continued. Any PLHIV co-infected with hepatitis B will receive additional TL if not already receiving entecavir *If contraindicated, use another NRTI backbone		
Second-line failure patients (2NRTI + PL) who need third-line ART		Darunavir 600 mg (BD) + Ritonavir 100 mg (BD) + DTG 50 mg (OD)

- ***Pneumocystis carinii*:** Causes mild-to-moderate pneumonia, severe pneumonia, disseminated disease.
- ***Prophylaxis and treatment*:** Trimethoprim/Sulfamethoxazole
- ***Toxoplasma gondii*:** Causes encephalitis, brain abscess, chorioretinitis, myocarditis.
  Treatment—sulfadiazine + Pyrimethamine + Folic acid.
- ***Isospora belli*:** Causes diarrhea
  Treatment—pyrimethamine
- ***Mycobacterium avium complex*:** Causes disseminated disease, may involve lung, bone marrow and liver.
  Treatment—Ethambutol + Rifabutin + Clarithromycin
- ***Mycobacterium tuberculosis*:** Active disease treatment–INH + Rifampicin + Pyrazinamide
- ***Candida albicans*:** Thrush, vaginitis
  Treatment—clotrimazole

- ***Cryptococcal neoformans*:** Causes meningitis, brain abscess, pneumonia, disseminated disease.
  Treatment—Amphotericin + Flucytosine followed by fluconazole.
- ***Isoplasma capsulatum*:** Treatment—amphotericin, itraconazole
- **Cytomegalovirus:** Retinitis, esophagus colitis and pneumonia.
  Treatment is ganciclovir.
- **Herpes simplex:** Recurrent perioral, peripheral or genital ulcers, esophagitis, acute retinal necrosis.
  Treatment is done with acyclovir.
- **Varicella zoster:** Cutaneous or retinal necrosis.
  Treatment is done with acyclovir.
- **Treponema pallidum:** Early syphilis late or neurosyphilis
  Treatment is with benzathine penicillin and probenecid for late syphilis.

As number of medications given to a patient increase, so do the chances of the drug reactions and interactions. The patient should be monitored for such reactions.

DRUG INTERACTIONS

- Zidovudine decreases the efficacy of stavudine. Hence, concomitant use is contraindicated.
- Concurrent administration of marrow suppressive agents increases the risk of toxicity.
- Coadministration of zalcitabine with didanosine is contraindicated.
- Rifampicin and ketoconazole are contraindicated in patients taking nevirapine. Also, nevirapine coadministration decreases indinavir, ritonavir, saquinavir levels as well as OCPs because induces CYP3A4.
- Enzyme inducer drugs—phenytoin, rifampin decreases delavirdine levels.
- Delavirdine increases plasma levels of saquinavir, indinavir, nelfinavir, ritonavir.
- Coadministration of efavirenz or nevirapine with saquinavir is contraindicated.
- Indinavir increases rifabutin levels and increases toxicity.
- Coadministration of protease inhibitors with ergot derivatives—midazolam, trizolam should be avoided, cause cardiac arrythmias or prolonged sedation.
- Indinavir and rifampin coadministration is contraindicated. (Rifampin induces CYP3A4 and decreases indinavir levels).

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Chapter
41

Use of Antimicrobials

- Injection ceftriaxione 1 g IV × 7 days in pneumonia. 2 g in meningitis.
- Tab metrogyl in anaerobic infections, per abdominal infections, neurocysticercosis (metronidazole + albendazole tablets).
- Meropenem in suspected infections when TLC > 12000. Dose—1 g IV 8 hourly.
- In amikacin 500 mg IV BD and metronidazole 100 ml IV 8 hourly × 7 days for Gram-negative infections and anaerobes in lung abscess, liver abscess.
- In methicillin resistant staphylococci infections (MRSA)—vancomycin 1.2 g IV BD, inj. linezolid 500 mg BD, inj. teicoplanin 1g IV BD.
- Injection tazobact (piperacillin + tazobactam) 4.5 g IV for TLC >13000 for Gram-negative and Gram-positive infections.
- For influenza—tab tamiflu 75 mg BD × 14 days, Swineflu—75 mg BD × 21 days.
- Benzathine penicillin G—in rheumatic heart disease (RHD) and infective endocarditis or syphilis. 1.2 million IU IM once every 3 weeks for 5 years as prophylaxis, in scarlet fever.
- Injection sulbactam 4.5 g TDS in high total leucolyte count and serious heart disorders.
- Tab cefradoxil in upper respiratory tract infection (URTIs) and chest infections.
- Tab cefuroxime in URTIs 250 mg BD and per abdominal infections. Cefoperazone sulbactam in chest infections and per abdominal (P/A) infections. Cefixime 500 mg IV BD in URTIs.
- Cefpodoxime proxetil 100 mg BD is used in respiratory disorders.
- Plain imipenem 500 mg IV BD if total lecucocyte count >13,000 and fever not subsiding with ceftriaxone.
- Adverse drug reactions are skin rash with meropenem, imipenem, convulsions with ceftriaxone.
- Clindamycin 600 mg IV BD in abscess.
- UTI—tab nitrofurantoin 400 mg BD × 14 days.
- Chronic UTI—triple drug therapy—nitrofurantoin + doxycycline + metronidazole. Doxycycline in atypical pneumonia.
- Abdominal TB is diagnosed by CT scan and X-ray, sputum for AFB for TB chest.
- In children, the antimicrobials should be used only for infective agents—*Shigella*, *Vibrio cholerae*, *E. histolytica*, *Giardia*. In dysentery–empiric treatment can be initiated with cortimoxazole or ampicillin for 5 days. If there is no improvement after 48 hours, resistance to initial antimicrobial is assumed and child should be given second-line antimicrobial, e.g. nalidixic acid 15 mg/kg/dose 4 times/day.

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Chapter
42

Treatment of Fungal Diseases

Fungal infections are superficial infections and systemic infections. Superficial mycosis are common and cause discomfort and are curable. The deep mycoses are serious infections difficult to treat.

Drugs used as antifungals are:

1. **Antifungal antibiotics**
   a. Polyene antibiotics—used by systemic route—amphotericin, used only topically—nystatin, hamycin, natamycin
   b. Heterocyclic benzofuran—griesofulvin effective only systemically
   c. Echinocandins—capsofungin
2. a. Imidazoles—used by both systemic and topical route—ketoconazole, used only topically—miconazole, clotrimazole, econazole, oxiconazole
   b. Triazoles—used by systemic route—fluconazole, itraconazole, used only topically—terconazole
3. Fluorinated pyrimidine, e.g. flucytosine
4. Allylamines—terbinafine—effective systemically and topically
5. Topical antifungal agents—tolnaftate, undecylenic acid, quinodochlor, benzoic acid, ciclopiroxolamine

The antifungal drugs act by inhibiting cell wall synthesis, e.g. echinicandins, increasing cell membrane permeability by binding with ergosterol, e.g. amphotericin B, nystatin; ergosterol synthesis inhibitors, e.g. imidazoles, triazoles, allylamines; nucleic acid synthesis inhibitors, e.g. 5-flucytosine; inhbit mitosis by acting on microtubules, e.g. griesofulvin.

Amphotericin B: It is drug of choice for systemic fungal infections such as mucormycosis, invasive aspergillosis, extracutaneous sporotrichosis, cryptococcosis, trichosporiosis, penicilliosis marneffei. It is also used in balstomycosis, histoplasmosis, coccidiomycosis in immunocompromised patients. It is used topically only for cutaneous, oropharyngeal and vaginal candidiasis. The toxicity due to IV infusion is fever, chills, muscle spasms, vomiting, headache and hypotension. On prolonged use, it is highly nephrotoxic. The liposomal form of amphotericin has reduced toxicity while maintaining efficacy. The dose is 3–5 mg/kg. For systemic therapy—1–1.2 mg/kg/day.

Nystatin—it is used only for cutaneous and vaginal candidiasis (1 lac unit twice a day).

Griesofulvin—is useful for fungal infections of skin, hair and nail caused by dermatophytes *Microsporum, Epidermophyton, Trichophyton*. It is fungistatic. The treatment duration depends on rate of turnover of infected keratinous tissue and site of infection. The daily dose is 500 mg for adults and for children 15 mg/kg/day in 4 divided doses. It is an enzyme inducer and increases the metabolism of warfarin and oral contraceptives.

Capsofungin—is used for deep and invasive candidiasis and as salvage therapy for invasive aspergillosis. It is also used for neutropenic patients with recurrent fever. The dose is 70 mg daily as slow IV infusion for 1 hour followed by 50 mg daily.

AZOLES

Ketoconazole: Accumulates in stratum corneum and used orally for dermatophytosis, used topically for tinea versicolor and seborrheic dermatitis as 2% cream, gel, shampoo. It is used orally for mucocutaneous, oral and esophageal and vulvovaginal candidiasis. 400 mg OD.

Fluconazole: Used for oropharyngeal candidiasis 200 mg on day 1 followed by 100 mg daily for 2 weeks, for vulvovaginal candidiasis 150 mg as single dose.

Itraconazole—is effective for blastomycosis, histoplasmosis, sporotrichosis. It is drug of choice for madura foot caused by *Actinomycetes*. 200 mg/day with meals for 3 months.

Voriconazole—is used for invasive aspergillosis and esophageal candidiasis. It is drug of choice for febrile neutropenia refractory to antibacterials. Prolongation of QTc interval may occur. Dose is 200 mg BD.

Posaconazole—is only azole active against zygomycosis or mucormycosis. Dose is 400 mg BD with meals.

Triazoles significantly cross blood–brain barrier and achieve good concentration in CSF and are used for fungal meningitis. All azoles are teratogenic on systemic use and avoided during pregnancy and lactation.

Antimetabolite-flucytosine—is oral use for cryptococcal meningitis 100 mg/kg/day in 4 divided doses with amphotericin for initial 2 weeks. 5 FC causes bone marrow depression/colitis.

ALLYAMINE

Terbinafine—oral use for onychomycosis/tinea capitis. Most effective drug in toenail infection. It is used topically for tinea cruris/corporis/pedis and tinea versicolor. 250 mg OD for 3 months.

Topical antifungals are used for superficial fungal infections limited to stratum corneum, squamous mucosa and cornea, e.g. dermatophytosis, candidiasis, tinea versicolor, fungal keratitis. These are ciclopirox olamine, tolnaftate, quinidochlor, undecylenic acid, benzoic acid, selenium sulphide, sodium thiosulphate.

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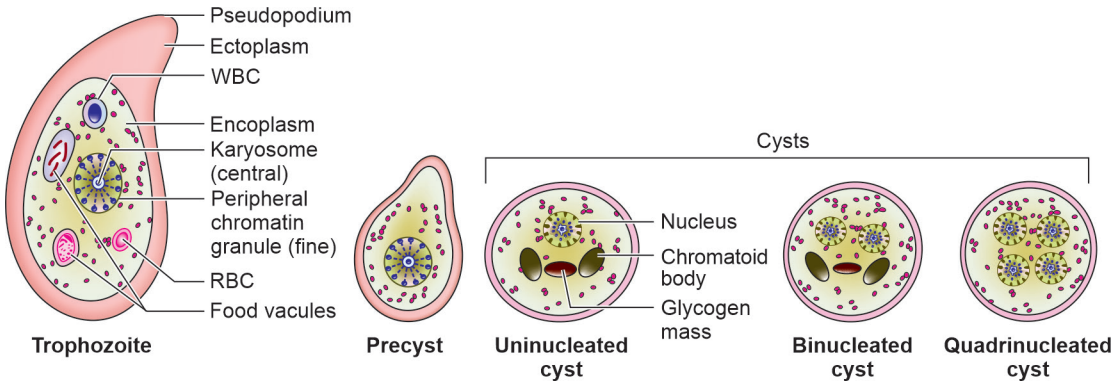
Chapter
43

Treatment of Amoebiasis and Other Protozoal Infections

AMOEBIASIS

It is infection with hemolytic *E. histolytica. E histolytica* can cause asymptomatic infection, mild-to-moderate colitis, severe intestinal infection, amoebema, liver abscess. Amoebiasis occurs when mature cysts are ingested and passed into colon where they divide into trophozoites. Small bowel lumen amoebiasis is asymptomatic and trophozoites are passed into feces. Treatment is directed at eradicating cysts with a luminal amoebicide (Fig. 43.1). In 1% cases, trophozoites invade the mucosa and form the ulcers—passage of mucus or blood in stools presenting as acute dysentery. Sometimes, the trophozoites enter the blood through the ulcer or from intestinal mucosa via the portal circulation and reach the liver and cause hepatic amoebiasis. Extraintestinal amoebiasis may also affect other organs like kidney, spleen, lungs and brain (Fig. 43.2).



Figs 43.1A to C: *Entamoeba histolytica* (schematic diagram): (A) Trophozoite; (B) precyst; (C) cysts

Treatment is with

1. Systemic or tissue amoebicide:
   a. For both intestinal and extraintestinal amoebiasis
      Nitroimidazoles—metronidazole, tinidazole, secnidazole, ornidazole, satranidazole
      Alkaloids from ipecacuanha—emetine and dehydroemetine
   b. Only for extraintestinal amoebiasis—chloroquine

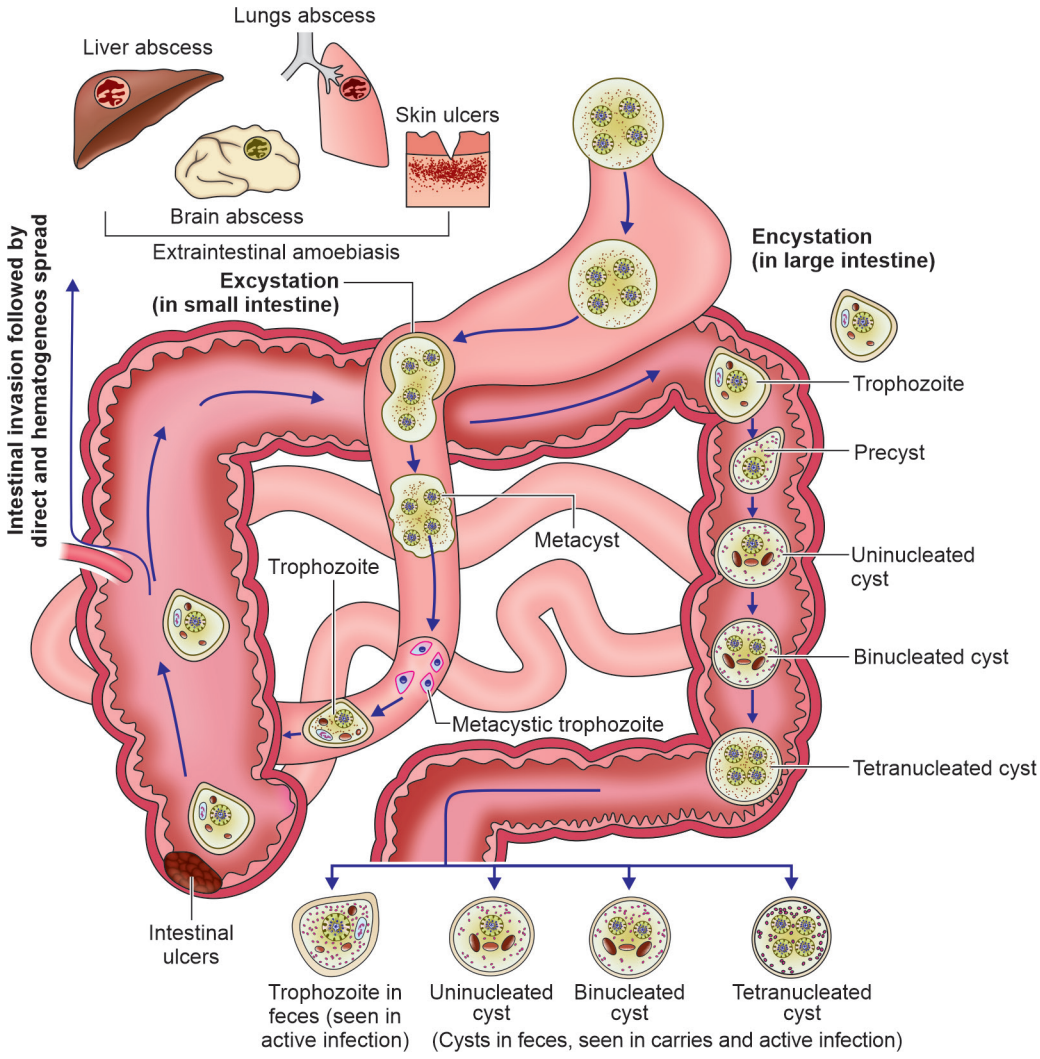


Fig. 43.2: Life cycle of *Entamoeba histolytica*

2. Luminal amoebicide
   a. Amide—diloxanide furoate, nitazoxanide
   b. 8-hydroxyquinoline
   c. Antibiotics—aminoglycosides—paramomycin, oxytetracycline

Metronidazole: Agent of choice for treating infections caused by *E. histolytica*, *Giardia lambia* and *Trichomonas vaginitis*. It takes up electron from bacteria and gets activated by reduction of nitro group. It kills trophozoites of *E. histolytica* but not the cysts. The dose for amoebiasis is 800 mg TDS for 7 days. For giardiasis, it is 200 mg TDS for 7 days. For trichomoniasis, 2 g single dose or 400 mg TDS × 7 days. Male partner has to be treated concurrently to prevent the recurrence.

It is also used in treating anaerobic bacterial infections: *Bactreroides fragilis* in pelvic and abdomen surgeries. IV 15 mg/kg followed by half dose every 6 hours. It is used in *Clostridium difficile* infection, *H. pylori* infection, non-specific vaginitis—2 g single dose, acute nectrotizing

ulcerative gingivitis. 400 mg TDS. The common adverse effects are nausea, headache, dry mouth, metallic taste. It is contraindicated in active CNS disease due to neurotoxicity, severe hepatic disease, blood dyscrasias, first trimester of pregnancy, in alcoholics due to disulfiram like reaction.

Tinidazole: Longer duration of action, so single dose used. 2 g OD in amoebiasis, trichomoniasis and giardiasis.

Secnidazole: 2 g single dose.

Ornidazole: Longer action. For chronic intestinal amoebiasis—300 mg BD for 5 days.

Satranidazole: More potent, 300 mg BD for 5 days for amoebiasis.

Diloxanide furoate: It is mainly used for asymptomatic cyst passers, after treating intestinal and extraintestinal amoebiasis to prevent relapse as it is active against the cysts not trophozoites. The dose is 500 mg TDS for 5–10 days.

Nitazoxanide: Acts by inhibiting enzyme pyruvate ferrodoxin oxidoreductase, important for electron transfer reaction in anaerobic organisms. It is mainly used for giardiasis. The dose is 500 mg × 3 days.

8-hydroxyquinolines—is used orally as luminal amoebicide and also for giardiasis and trichomoniasis. The dose of clioquinol is 250–500 mg TDS for 2 weeks, iodoquinol-650 mg TDS × 2 days.

Antibiotics

Paromomycin—is useful for treatment of intestinal amoebiasis, 25–35 mg/kg/day in 3 divided doses × 7 days. It is safe during pregnancy and can be used to cure amoebiasis and giardiasis.

Tetracyclines: The alterations of gutflora by tetracyclines also inhibit the growth of *E. histolyica* in colon. They are used as adjuvants with directly acting luminal amoebicides in chronic cases of non-invasive intestinal amoebiasis.

LEISHMANIASIS

It is caused by *Leishmania donovani* spread by bite of female sandfly. The common form is called kala-azar also called visceral leishmaniasis and spreads through bloodstream leading to hepatomegaly, splenomegaly, anemia and fever (Fig. 43.3).

Treatment

Pentamidine—is only administered parentrally. Inhaled as nebulised powder for prevention of pneumocystosis. Pentamidine is used as alternative therapy for pulmonary and extrapulmonary disease caused by pneumocystis carinii. Its alternative agent for primary and secondary prophylaxis against pneumocystosis in immunocompromised individuals–including patients with advanced AIDs, used for African trypanosomiasis (sleeping sickness) and visceral leishmaniasis (2–4 mg/kg IM daily or every day upto 15 doses). Systemic pentamidine is highly toxic drug with IM injection, pain at injection site is common.

Sodium stibogluconate—is first-line agent for cutaneous and visceral leishmaniasis. Treatment given once daily at dose of 20 mg/kg/day IV/IM for 20 days in cutaneous leishmaniasis and 28 days in visceral and mucocutaneous disease. IM injections are painful.

Liposomal amphotericin: The cure rate is 99%. 10 mg/kg IV infusion as single dose.

Miltefosine—is highly effective orally in cutaneous and visceral leishmaniasis. The adult dose is 100 mg OD for 12 weeks for post-kala-azar dermal leishmaniasis. Should not be given during pregnancy.

Paromomycin—can be used alone or as addon to other drugs. 15 mg/kg per day for 3 weeks.

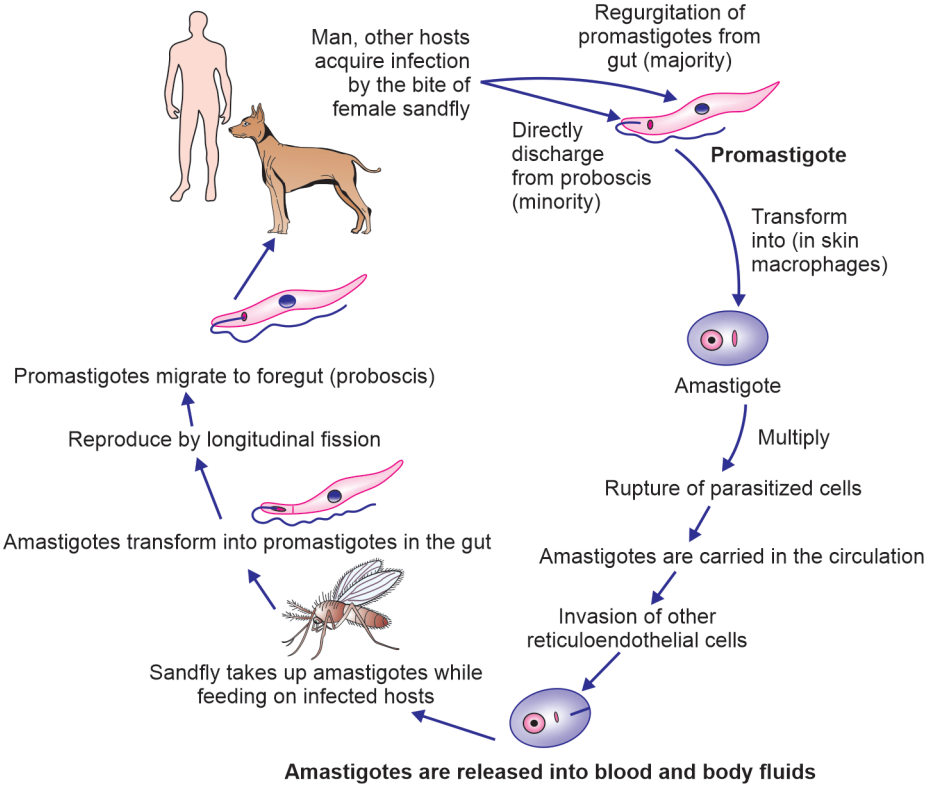

Man, other hosts acquire infection by the bite of female sandfly
Regurgitation of promastigotes from gut (majority)
Directly discharge from proboscis (minority)
Promastigote
Transform into (in skin macrophages)
Amastigote
Multiply
Rupture of parasitized cells
Amastigotes are carried in the circulation
Invasion of other reticuloendothelial cells
Amastigotes are released into blood and body fluids
Sandfly takes up amastigotes while feeding on infected hosts
Amastigotes transform into promastigotes in the gut
Reproduce by longitudinal fission
Promastigotes migrate to foregut (proboscis)

Fig. 43.3: Life cycle of *Leishmania donovani*

TOXOPLASMOSIS

It is caused by *Toxoplasma gondii*. Treatment is with pyrimethamine and sulfadiazine or pyrimethamine and clindamycin. Alternative treatments are clindamycin or clarithromycin/azithromycin or dapsone or spiramycin or triamtrexate + cortimoxazole or pyrimethamine + folinic acid.

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Chapter
44

Anthelmintic Drugs

The humans are infected by 3 helminths—Nematodes, trematodes and cestodes. They infect the intestine as well as blood and tissues. Antihelmintic drugs are those that either kill (vermicide) or remove or eliminate (vermifuge) infesting helminths. The treatment is chosen depending not only on efficacy, but also on lack of side effects/toxicity, convenient administration and affordable cost. The clinical use of anthelmintics has not led to resistance.

Nematodes—are elongated roundworms possessing a complete digestive system (Fig. 44.1).

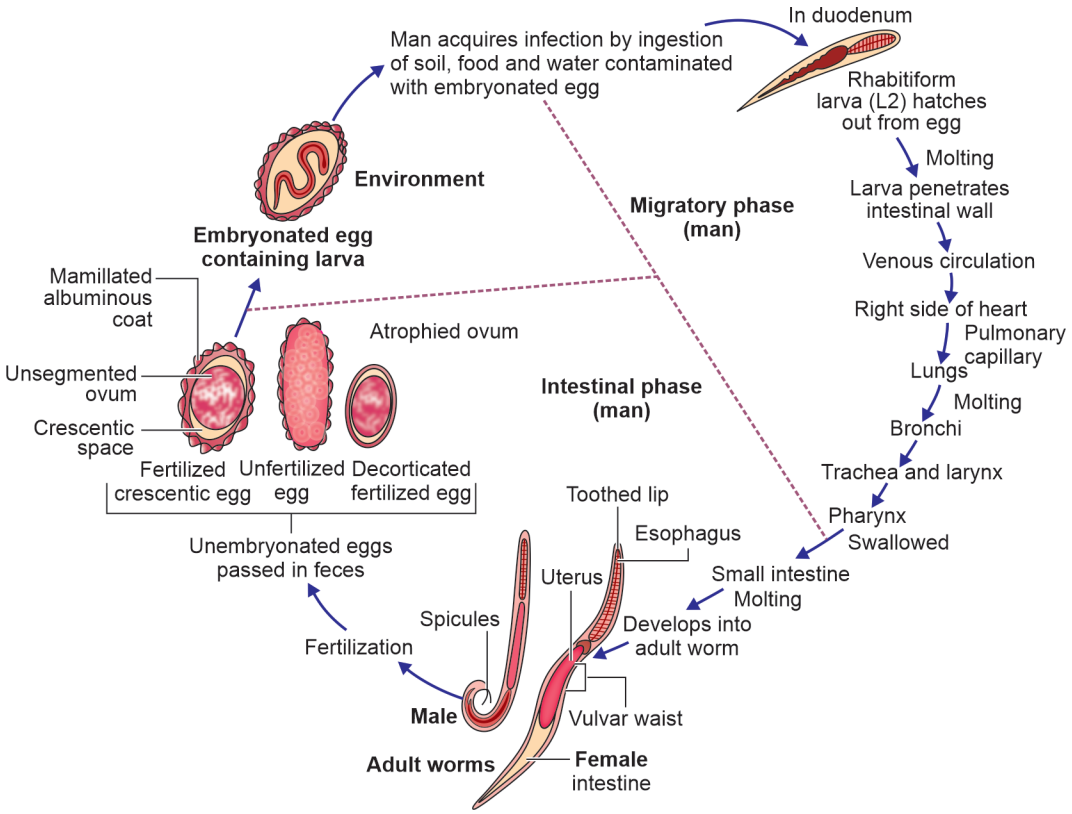

Fig. 44.1: Life cycle of ascaris lumbricoides

Mebendazole is first-line agent for the treatment of infections caused by whipworms (*Trichuris trichura*), pinworms (*Enterobius vermicularis*), hookworms (*Necator americanus* and *Ancylostoma duodenale*) and roundworms (*Ascaris lumbricoides*). The dose is 100 mg BD for 3 consecutive days. Mebendazole and benzimadoles bind to β-tubulin of the parasite and inhibit microtubule polymerization in the parasite, expelling the parasite in faeces.

Albendazole—used in curing roundworm, hookworm, threadworm and whipworm (trichuriasis) in children. 400 mg OD in adults. To treat *Trichinella spiralis*, 400 mg OD for 3 days. It is drug of choice for hydatid disease and neurocysticercosis 400 mg BD for 4 weeks. The side effects can be nausea, diarrhoea, abdominal pain, headache, dizziness.

- **Pyrantel pamoate** is useful in the treatment of infections caused by roundworms, pinworms and hookworms. It causes release of ACh and inhibition of cholinesterase leading to paralysis of the worm and subsequent expulsion. It is used as single dose 11 mg/kg for ascariasis and enterobiasis, and same dose for 3 days for ancylostomiasis and strongyloidiasis.
- **Piperazine** causes flaccid paralysis and expulsion of worm by peristalsis. The dose in adults and children >12 years is 2 g daily for 7 days.
- **Tetramisole and** its optical isomer levamisole are used for treatment of ascariasis and ancylostomiasis. Neural stimulation in the worm causing tonic paralysis is the mechanism of action. Adult dose is 150 mg and 50 mg for children <20 kg in tropical pulmonary eosinophilia.
- **Diethylcarbamazine citrate (DEC)**—is cidal to microfilaria. It is first-line drug for filariasis. Diethylcarbamazine is a drug of choice for filariasis caused by infection with nematode *Wuchereria bancrofti*, *Brugia malayi*. It kills the microfilaria and has activity against adult worms. The dose for treatment of filariasis is 6 mg/kg for 2 weeks. It is also used in the treatment of tropical pulmonary eosinophilia. The dramatic improvement in the signs and symptoms of eosinophilic lung or tropical eosinophilia is produced by DEC for 2–3 weeks. The typical Mazzotti reaction may occur within a few hours of the first dose.

DRUGS FOR TREATMENT OF CESTODES

Life cycle of *T. solium* is shown in Fig. 44.2.

Cestodes or tapeworms have flat segmented body and attach to the host's intestine.

Niclosamide—is an effective drug used for treatment of teniasis, diphollbothriasis and other cestode infections. It lethally inhibits the mitochondrial phosphorylation of ADP in the parasite. A laxative is given prior to oral administration purges the bowel of all dead segments and enhances, digestion and liberation of ova. The dose is 2 g 2 tab after meals followed by another tab after one hour.

Praziquentel—is an agent of choice for the treatment of all the tapeworms except echinococcus and all the flukes except *Fasciola hepatica*. It increases the permeability of the cell membrane to calcium causing contracture and paralysis of the parasite. The dose for tapeworm infections is 10–20 mg/kg as single dose. For blood flukes, single dose of 40 mg/kg and for intestinal and liver flukes 3 doses of 25 mg/kg 6 hourly on same day. It is the second choice drug for cysticercosis and neurocysticercosis.

- It is not used for the treatment of ocular cysticercosis as destruction of the organism may cause irreversible damage to the eye.

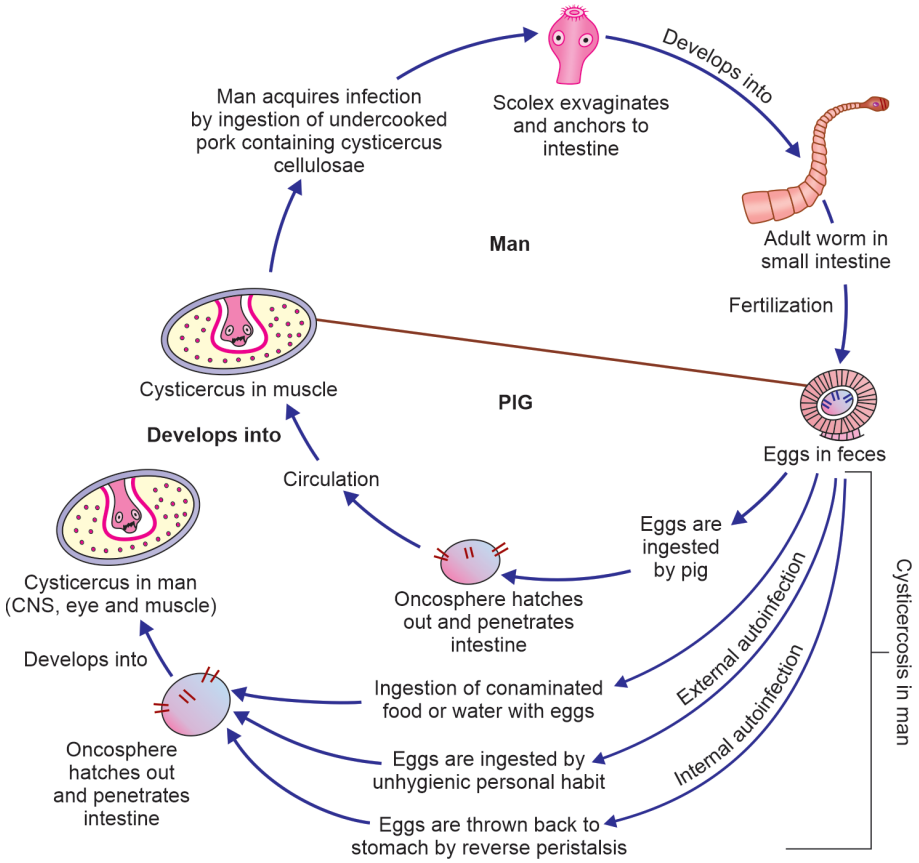
Man acquires infection by ingestion of undercooked pork containing cysticercus cellulosae
Scolex exvaginates and anchors to intestine
Develops into
Adult worm in small intestine
Man
Fertilization
Cysticercus in muscle
PIG
Develops into
Eggs in feces
Circulation
Eggs are ingested by pig
Cysticercus in man (CNS, eye and muscle)
Oncosphere hatches out and penetrates intestine
Develops into
Ingestion of conaminated food or water with eggs
External autoinfection
Internal autoinfection
Cysticercosis in man
Oncosphere hatches out and penetrates intestine
Eggs are ingested by unhygienic personal habit
Eggs are thrown back to stomach by reverse peristalsis

Fig. 44.2: Life cycle of *T. solium*

Albendazole—inhibits synthesis of microtubule and uptake of glucose in nematodes, used in cysticercosis and hydatid disease. It is metabolized in liver and metabolites excreted in bile.

Ivermectin

Used for treatment of lymphatic filariasis and onchocerciasis, is also used in treatment of pediculosis-lice and scabies. Ivermectin acts by paralyzing the worms by binding to glutamate gated chloride channels and also enhancing GABA activity and enhances the permeability of the cell membrane to chloride ions leading to hyperpolarization and paralysis. The single dose of 150 µg/kg every 6–12 months is for onchocerciasis. For lymphatic filariasis, single dose of 400 µg/kg/year for mass chemotherapy of filarial infection. It acts only on microfilariae and not on the adult worm. The main toxicity is Mazotti reaction. Mild itching, swollen and tender lymph nodes.

Resistance to anthelmintic drugs: The extensive use of anthelmintic drugs in farming is one of the contributory factors for the development of resistance. Resistance can result from efflux of the drug by P-glycoprotein transporter, reduced affinity for binding of drug as in benzimadoles to the b tubulin, modification of the structure of the binding site.

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Chapter
45

Treatment of Leprosy

Infection with bacterium, *Mycobacterium leprae* leads to leprosy. Leprosy can be treated effectively with dapsone and rifampin, adding clofazimine in multibacillary cases.

DRUGS USED IN LEPROSY

- Sulfone—dapsone
- Phenothiazine derivative—clofazimine
- Antitubercular drugs—rifampin, ethionamide
- Other antibiotics—ofloxacin, moxifloxacin, minocycline, clarithromycin
- Leprosy is a chronic granulomatous infection caused by mycobacterium leprae .and more prevalent in lower socioeconomic strata. Leprosy manifests in tuberculoid and lepromatous forms with intermediate clinical presentations. The most widely used classification of leprosy is that of Ridley and Jopling into—lepromatous (LL), borderline lepromatous (BL), mild borderline (BB), borderline tuberculoid (BT) and tuberculoid (TT).
- WHO divided leprosy into paucibacillary leprosy—patients have few bacilli and is non-infectious. It includes TT and BT and indeterminate types.
- Multibacillary leprosy—patient has large bacillary load and is infectious. It included the LL, BL and BB types.

WHO reclassified leprosy in 1998 into:

- Single lesion paucibacillary leprosy (PBL) with a solitary cutaneous lesion.
- Paucibacillary leprosy with 2–5 skin lesions, no nerve or only 1 nerve involvement, smear negative
- Multibacillary leprosy (MBL) with 6 skin lesions as well as all smear positive cases, >1 nerve involvement

Pathophysiology and clinical features: Mycobacterium leprae infect Schwann cells and skin macrophages. In tuberculoid leprosy, γ-interferon is produced by T cells that mediate the action of macrophages in killing *M. leprae*. In lepromatous leprosy, the action of macrophages is facilitated by the IL4. The onset is gradual. The most common symptom is small but persistent area of impaired sensation or numbness. In other patients the first noticeable feature may be macules, which are hypopigmented and erythematous (Figs 45.1 and 45.2). The disease may also be present acutely in a lepra reaction with neuritis, iritis or erythema nodosum leprosum.

Fig. 45.1: Leprosy (*Image courtesy*: Department of Dermatology, OPD, Government Doon Medical College)

Fig. 45.2: Leprosy—skin lesions

- **Leprosy damages the body in 3 ways**—Peripheral neuritis–leads to sensory, motor and autonomic dysfunctions. Sensory loss permits trauma from pressure, friction, burns and cuts. Autonomic nerve damage causes dry skin which cracks easily and heals slowly. Secondary bacterial infection in an anesthetic unprotected limb leads to cellulitis, osteomyelitis and gross tissue destruction.
- Bacillary load damages the infiltrated organs, affects skin and nerves, causes testes atrophy, impotence and gynecomastia, affects mucosa of nose, mouth, pharynx and larynx—rhinitis, hoarseness, perforation of nasal septum, palate, laryngeal obstruction, cystic lesions of phalanges leads to fractures, loss of upper incisors and nasal spine leading to nasal collapse, in eye—keratitis, iridocyclitis, corneal anesthesia leading to blindness.
- Tuberculoid leprosy has few hypopigmented lesions, macules. The nerve supplying the skin lesion may be enlarged.
- In lepromatous leprosy, nodular lesions appear on the ears and face and eyebrows are lost. Diffuse symmetrical thickening of the skin causes thickened brow and lobes of the ear. Clinical evidence of nerve damage occurs late in lepromatous leprosy. Anesthesia and anhidrosis are first detected in the distal aspects of the forearms and lower legs in a glove and stocking distribution and eventually over trunk and face.
- **Anesthesia**—local sensory loss and loss of sweating in areas where small dermal sensory and autonomic nerve fibres are damaged. Peripheral nerve trunks are affected with regional sensory loss and muscle dysfunction. Blindness can occur, involves facial nerve and trigeminal nerve.

DRUGS USED IN LEPROSY

- **Dapsone**—is bacteriostatic for *M. leprae*. The dose is 100 mg/day. Adverse reactions include hemolysis, methemoglobinemia and peripheral neuropathy
- **Rifampicin**—is the most potent bactericidal drug for *M. leprae*. It is given as 600 mg dose once monthly, in multidrug therapy and is practically non-toxic and does not induce enzymes to affect metabolism of other drugs. It is contraindicated in patients with hepatic and renal impairment and erythema nodosum leprosum and reversal reaction in leprosy patients.
- **Clofazimine**—is given as part of multidrug therapy of leprosy. It is orally active, accumulates in macrophages and accumulates in many tissues like subcutaneous fat as needle shaped crystals. The major disadvantage is red and dark skin within few weeks of use. Discoloration of hair and body secretions may also occur. The GIT symptoms are nausea, anorexia, abdominal pain, weight loss, enteritis. It should not be given during early trimester of pregnancy and in patients with liver or kidney disease. After few months of leprosy, deposition of clofazimine crystals in the submucosa occurs.
- **Multidrug therapy (MDT)**
  - **MDT for multibacillary:** Rifampin 600 mg once a month supervised, dapsone 100 mg daily self-administered, clofazimine 300 mg once a month and 50 mg daily self-administered, total duration 12 months.
  - **MDT for paucibacillary:** Rifampin 600 mg once a month supervised, dapsone 100 mg daily, total duration for 6 months.
- **Fluoroquinolones:** Many fluoroquinolones like ofloxacin, pefloxacin, moxifloxacin, sparfloxacin are highly active against *M. leprae*. Clinically ofloxacin or moxifloxacin is used. The fluoroquinolones hasten the bacteriological and clinical response, being part of multidrug therapy. They are bactericidal to *M. leprae.* They can be used as an alternative drug instead of rifampicin to cut down the period of treatment and reduce chances of drug resistance. The dose is 400 mg/day.
- **Minocycline:** Being lipid loving, this tetracycline penetrates into *M. laprae* and is active against them. A dose of 100 mg/day produces peak blood levels exceeding minimum inhibitory concentration (MIC) 10–20 times against *M. leprae*. Its antileprosy activity is lesser than that of rifampin but greater than that of clarithromycin. It has good clinical response in lepromatous symptoms. Vertigo is the only serious complication.
- **Clarithromycin**—is the only macrolide antibiotic with significant activity against *M. leprae*. Monotherapy with clarithromycin 500 mg daily causes 99.9 % bacterial killing in 8 weeks. It synergises with minocycline.
- National leprosy eradication programme (NLEP) and WHO recommend that paucibacillary lepromatous cases should be treated with dapsone, rifampin for 6 months, while multibacillary lepromatous cases with dapsone + rifampin + clofazimine for 2 years or till disease inactivity/skin smear negativity is achieved.
- **Prophylaxis of leprosy:** Leprosy spreads by skin-to-skin contact mainly from the patients of MB leprosy with open lesions and with pus. Rarely, spread may occur through the droplet from respiratory passage with severe MB leprosy. Thus prevention is by avoiding skin contact with patients. BCG vaccine may offer some protection against leprosy.

- There are two types of lepra reactions with treatment of dapsone.
  - **Lepra reaction type 1**—occurs in patients with tuberculoid leprosy, due to delayed hypersensitivity to antigen of *M. leprae*. The manifestations are cutaneous ulcerations and peripheral nerve function deficit. Mild cases can be treated with NSAIDs like PCM and aspirin. Early treatment is given with corticosteroids and clofazimine. Prednisolone 40–60 mg daily is tapered gradually over a period of 2–3 months.
  - **Lepra reaction type 2**—is possibly arthus type of reaction that occurs in patients of lepromatous leprosy with dapsone. It is of abrupt onset, existing lesions enlarge, become red, inflammed and painful. It is seen after 4–6 weeks, due to humoral antibody response to dead bacteria. Mild cases can be treated with NSAIDs like PCM, aspirin. This reaction is treated by clofazimine or corticosteroids (prednisolone 40–60 mg per day). Dapsone should not be stopped nor the dose be reduced in both type of lepra reactions. Clofazimine is used initially 100 mg TDS × 12 weeks followed by 100 mg BD × 12 weeks and then 100 mg OD for 12–24 weeks.

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Chapter
46

Treatment of Sexually Transmitted Diseases

- Sexually transmitted infections (STIs) are caused by sexual contact transmitted by bacteria, viruses or parasites. Infection can pass from human to human in blood, semen or vaginal and other body fluids. STIs can spread to infants during pregnancy or childbirth or blood transfusions or shared needles.
  If latex condoms are used, it greatly reduces the risk of catching or spreading STDs.
- The patient is generally asked for history focusing on genital symptoms—genital ulceration, rash, itching, pain or swelling and urinary symptoms especially burning on micturition. The men are asked about presence of urethral discharge. In women, vaginal discharge and contact history is enquired.
- **Gonorrhoea**—is caused by bacteria called *Neisseria gonorrhoae*, by Gram-negative diplococcus. Gonorrhoea is passed on through unprotected sex or by sharing sex toys. *Neisseria gonorrhoeae* infects columnar epithelium in the lower genital tract, rectum, pharynx and eyes.
- The symptoms of disease normally appear within 10 days of infection but they can occur many months later. Roughly 10% of men and 50% of women hardly experience any symptoms. The infected women complaint of unusual vaginal discharge, thick and green or yellow in colour. Also, there is pain on urination, lower abdominal pain, interperiods bleeding or bleeding after sex. In men, they suffer from acute urethritis with a mucopurulent discharge containing gonococci in large numbers (Fig. 46.1).
- Gonorrhoea is a venereal disease that has been known since ancient times, termed by Galen in 130 AD. The first stage of infection relates to adhesion of gonococci to the urethra or other mucosal surfaces by means of pili. It adheres rapidly so that micturition after exposure offers no protection against infection. By third day of infection, the cocci penetrate through intercellular spaces and reach the subepithelial connective tissue.
- Complications in males, the infection spreads through urethra to the prostate, seminal vesicles and epididymis. Chronic urethritis can cause strictures. The infection may spread to the periurethral tissues, causing abscesses and multiple discharging sinuses (Watercan perineum).
- In women, the initial infection involves the urethra and cervix uteri. The infection may spread to bartholin glands, the endometrium and the fallopian tubes. Pelvic inflammatory disease and salpingitis may cause sterility. Rarely, peritonitis may develop with perihepatic inflammation. (Fitz-Hugh-Curtis syndrome). Many women may carry gonococci in the cervix without any symptoms.

- **Prognosis:** The symptoms usually resolve without treatment but its not known how long the patient remains infectious. Delay in treatment leads to epididymo-orchitis, salpingitis and pelvic infection, perihepatitis, right hypochondrial pain and tenderness.
- Bacteremia causes fever, joint pain, peripheral pustular rash.
- Acute gonococcal arthritis (Fig. 46.2).
- Acute purulent conjunctivitis, ophthalmia neonatorum in infants born to infected mothers.

Fig. 46.1: Gonococcal urethritis

Fig. 46.2: Gonococcal arthritis

- *Pelvic inflammatory disease* (P1D): Infection of the uterus, ovaries and fallopian tubes. PID is generally occurs in 10–20% of untreated cases of gonorrhoea. Several pathogens can cause PID including *Chlamydia trachomatis, Neisseria gonorrhoae* and *Mycoplasma hominis*. On physical examination, lower abdominal pain is usually bilateral, and vaginal examination reveals adnexal tenderness with or without cervical discharge. Differential diagnosis is ectopic pregnancy.
  - During pregnancy, Gonorrhoea can cause abortions and premature labour if mother is infected during pregnancy. The baby can be born with conjunctivitis and should be treated with antibiotics.
  - In men, gonorrhoea can cause epididymitis causing swelling and tenderness in the scrotum. It can lead to infertility.

– In rare cases, untreated gonorrhoea can spread to other parts of the body causing inflammation of joints and tendons, skin irritation and redness, inflammation around the brain and spinal cord or the heart.

SUMMARY

When the infection spreads systemically, disseminated gonococcal infection occurs. Proctitis occurs in both sexes. It may develop by contiguous spread in women but in men it is result of anal sex. Conjunctivitis may occur, due to autoinoculation by fingers. The primary site of infection spreads by bloodstream to lead to metastatic lesions such as arthritis, ulcerative endocarditis and rarely, meningitis. Gonococcal bacteremia leads to hemorrhagic papules and pustules on the hands, feet and legs and to tenosynovitis and suppurative arthritis usually of the knees, ankles and wrists.

Diagnosis is by collecting urethral discharge, endocervical swab. The urethral discharge contains gonococci in large numbers. The specimens can be cultured in Stuart's medium and Mueller Hinton agar. In chronic infections, use Thayer Martin media. Polymerase chain reaction molecular methods has improved the sensitivity of the assay.

- The center for disease control and prevention has introduced the following treatment: Ceftriaxone 125 mg IM single dose, with 1 g azithromycin single dose or with doxycycline 100 mg twice a day for 7 days. The treatment is costly and proves good for co-existing chlamydial infection.

Gonococcal ophthalmia neonatorum: It is a bilateral conjunctivitis of neonates marked by copious purulent discharge, marked conjunctival chemosis and swelling of lids. The disease is contacted from the mothers having infected genitourinary tract by *Neissearia gonorrhoae*. It manifests in 1st week after birth as watery secretion which becomes purulent involving both eyes. The infant's condition is irritable due to his intensely inflamed conjunctiva, being chemotic and red. The bulbar conjunctiva bulges around the lids and cornea appears to be situated at the bottom of crater like pit. Due to invasion of intact corneal epithelium by the organism, corneal ulceration develops (Fig. 46.3).

Treatment of ophthalmia neonatorum: The eyes must be irrigated with warm saline 4 times a day. The standard regimen is instillation of penicillin drops 5000 to 10,000 units/

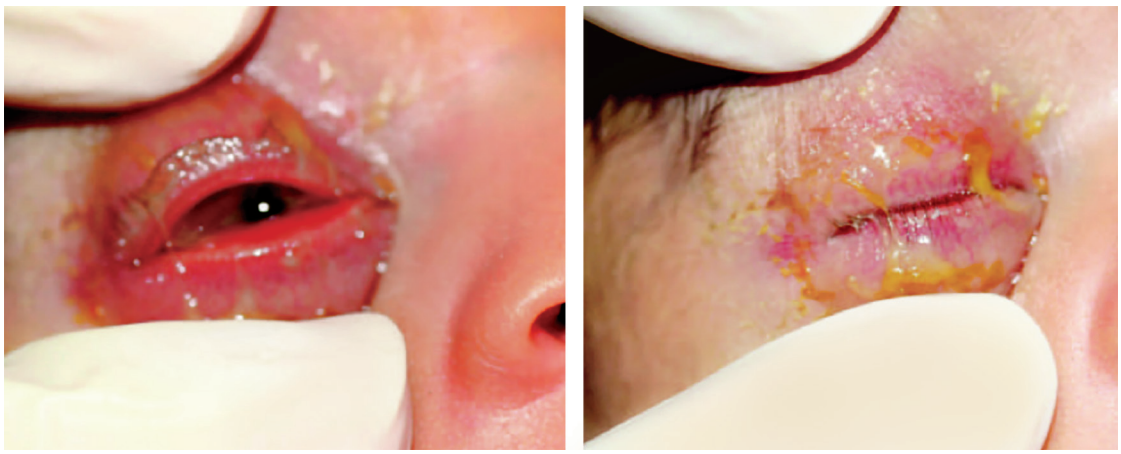

Fig. 46.3: Gonococcal ophthalmia neonatorum

ml every min for half an hour and then every 5 min for another half hour and then ½ hourly instillations. Systemic therapy should be started for 7 days in newborns with gonococcal ophthalmia neonatorum with ceftriaxone/cefotaxime/ciprofloxacin/or crystalline benzyl penicillin.

Syphilis: Syphilis can be acquired by the venereal or non-venereal route or congenital or acquired route. Venereal syphilis is a sexually transmitted infection caused by a type of bacterium known as *Treponema pallidum*. According to the centres for disease control and prevention, more than 88,000 cases of syphilis were reported in the United States in 2016. The rate of women with syphilis has been declining in the US but among men has been rising.

- **The four stages of syphilis are:** Primary, secondary, latent syphilis, tertiary syphilis.
- The spirochete enters the body through minute abrasions on the mucosa or skin. The patient infects the sexual partner maximally during the first two years of the disease. The infective dose is small as few 60 treponemes are capable of infecting 50% of human volunteers. The clinical disease has an incubation period of 10–90 days.
- Primary syphilis occurs about 3–4 weeks after a person contacts the bacteria. It begins with a small round sore called chancre which is painless but is highly infectious. This sore may appear on entering of bacteria inside the body such as on or inside the mouth, genitals or rectum. Syphilis is transmitted by direct contact with a sore during sexual activity including oral sex. The regional lymph nodes are moderately enlarged, mobile, discrete, rubbery, painless and non-tender.

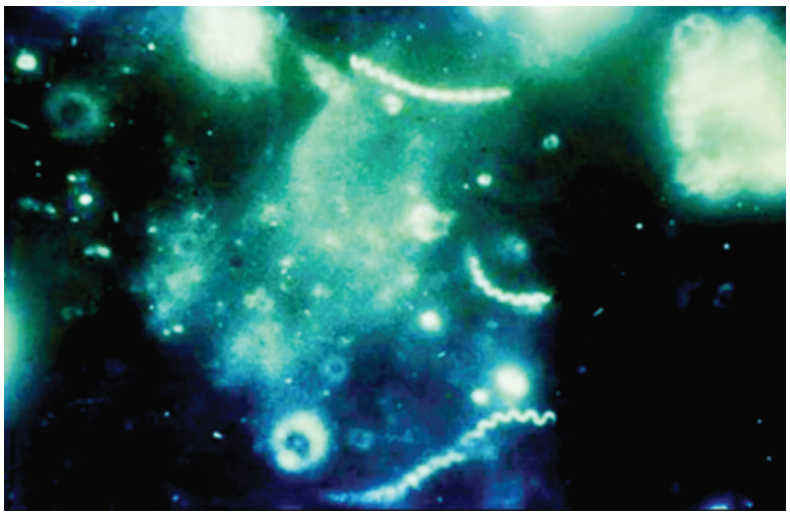

Fig. 46.4: Microscopy of *Treponema pallidum*

Secondary syphilis: 6–8 weeks after the development of chancre, the patient presents with mild fever, malaise and headache. The secondary stage is characterized by skin rashes and a sore throat. The rash wont itch and is usually found on palms and soles but it may occur anywhere on the body (Figs 46.4 to 46.6). Mucosal ulcers may affect the genitals, mouth, pharynx and larynx. Early lesions are superficial, later they develop a white base, red margin and coalesce to form snake track ulcers. Other associated symptoms of secondary syphilis may include headache, swollen lymph nodes, fatigue, weight loss, hair loss and aching joints.

Fig. 46.5: Syphilis lesion on palms

Fig. 46.6: Lesions on tongue

Latent syphilis: The manifestations of syphilis resolve after 4–12 weeks, the patient is asymptomatic.

Tertiary syphilis: It is the destructive stage of the disease. In untreated patients, appears after many years. Gummas or granulomatous lesions of syphilis occur on skin and mucosal surfaces and in bone. It can progress to blindness, deafness, mental illness, memory loss, destruction of soft tissue and bone, neurological disorders such as stroke or meningitis, heart disease, neurosyphilis causing an infection of the brain or spinal cord. CVS syphilis and neurosyphilis may take longer to develop and may lead to death.

Treatment of syphilis: Primary and secondary syphilis are effectively treated with a single dose of 2.4 million units benzathine penicillin IM into each buttock. Doxycycline 100 mg BD or erythromycin orally for 2 weeks may be used for penicillin allergic patients.

- Early and latent syphilis is treated with daily IM injection of 1.2 MU of procaine penicillin for 10 days or with 1–3 weekly doses of 2.4 MU benzathine penicillin. For late latent syphilis, benzathine penicillin 2.4 MU weekly for 4 weeks.
- Neurosyphilis should be treated with procaine penicillin 2.4 megaunits of IM once daily for 17 days with oral probenecid 500 mg 4 times a day.

Congenital syphilis: The fetus is affected by placental transfer of *T. pallidum* and fetal damage occurs after fourth month of gestation. Untreated maternal infection may lead to fetal loss, prematurity, neonatal death. A less severely affected baby has vesicles, bullae and mucosal ulcers at birth and disease of bones, joints, liver, kidneys and other organs. The specific treponemal hemagglutination assay is specific treponemal antigen test.

- Congenital syphilis in newborn should be treated with procaine penicillin 50,000 U/kg IM once daily for 10 days.
- **Anogenital herpes simplex:** Due to herpes simplex virus spread by sexual contact. The first attack is severe followed by milder recurrences. It may be suppressed by continuous oral acyclovir 400 mg twice daily. Infection is with herpes simplex 1 or type 2. The first symptom presentation is irritable vesicles rupturing to form small tender ulcers on the external genitalia. Lesions at urethra, vagina, cervix, perineal area, anus or rectum may cause dysuria, urethral or vaginal discharge, anal, perineal or rectal pain. The lymph nodes in the inguinal area become enlarged and tender (Fig. 46.7).
- The 1st attack presents with malaise, fever and local irritation followed by widespread painful tender vesicles affecting the genitals and rarely the anorectum. The vesicles rupture leaving painful tender erosions followed by crops of lesions. There may be nerve root pains in the second and third sacral dermatomes.
- The recurrent have 1 cluster of lesions covering 1 cm^2 which heals in 7–10 days. Lesions always heal and local saline bathing may be all necessary.

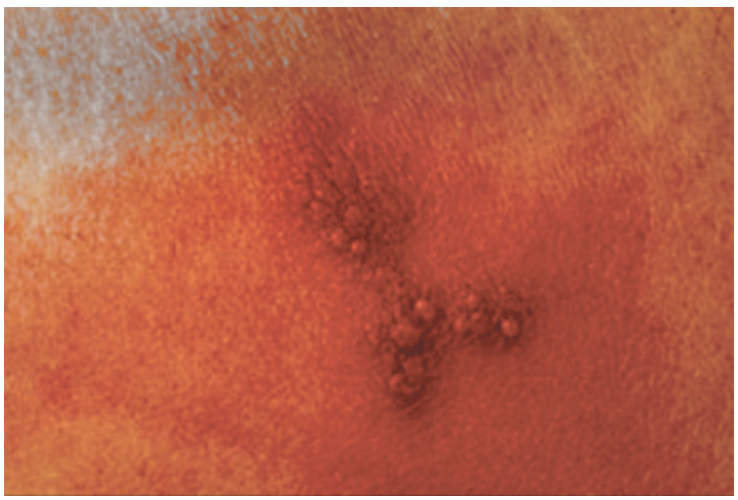

Fig. 46.7: Anogenital herpes simplex

Treatment of Genital Herpes

- Acyclovir 200 mg 5 times daily for 5 days orally inhibits viral replication and shortens first attacks. Recurrence may be suppressed by continuous oral acyclovir 400 mg twice daily In severe cases 5 mg/kg IV infused over 1 hour repeated 8 hourly for 10 days. Valacyclovir 0.5–1 g BD × 10 days. Famciclovir 250 mg TDS × 5 days.

Genital Warts

- HPV6, HPV 11, HPV 16 and HPV 18 infect the genital tract through sexual transmission. Warts due to HPV are common on the genitals and anus (Fig. 46.8a). HPV infection predisposes to carcinoma of the cervix.
- Common warts appear initially as smooth skin-colored papules which enlarge, becoming of irregular surface and hyperkeratotic producing warty appearance.
- Treatment is with 10–25% podophyllin applied weekly or 0.5% podophyllotoxin applied twice daily for 3 regular days/week for maximum of 5 weeks. Alternative methods are destruction by cryotherapy, electrocautery or laser. Warts tend to recur, so all patients must be followed up to ensure cure.

Molluscum contagiosum is caused by virus *Molluscum contagiosum*, produces small shiny papules with a central depression which allows differentiation from warts (Fig. 46.8b). Treatment is by destruction with cryotherapy or electrocautery.

Hepatitis B is transmitted readily between homosexual men but rarely between heterosexuals.

(a) Warts anogenital (b) Molluscum contagiosum

Fig. 46.8: Genital warts

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Chapter

47

Treatment of Septicemia and Antimicrobials for Systemic Therapy

Septicemia is a life-threatening condition when body's response to infection causes inflammation throughout the body leading to cascade of changes damaging multiple organ systems which fail even resulting in death. In a shocked patient, survival rate falls by 7% for each hour of delay in commencing effective antibiotics. Hospitalisation is done in cases of sepsis and treatment done with antibiotics, managing blood flow to organs and killing the infecting organism. The symptoms of septicemia start quickly making the patient look very sick. Patient has chills, fever, fast breathing, rapid heart rate. As it progresses, it leads to confusion, nausea, vomiting, red dots on skin, reduced urine volume, inadquate blood flow, shock. It can cause complications like septic shock and acute respiratory distress syndrome.

Treatment of Septicemia

When septicemia follows gastrointestinal or genital tract surgery—*E. coli*, anaerobic bacteria, e.g. bacteroides, streptococci or enterococci are likely pathogens, Piperacillin–tazobactam or gentamycin plus benzyl penicillin plus metronidazole are treatment drugs.

- Septicemia related to urinary tract infection usually involves *E. coli*, enterococci. Treatment is with gentamycin plus benzylpenicillin or piperacillin–tazobactam alone.
- Neonatal septicemia is usually due to Lancefield Group B *Streptococcus* or coliforms: Treatment with benzyl penicillin plus gentamycin or (vancomycin + ceftazidime)
- Staphylococcal septicemia may be suspected when there is an abscess, e.g. of bone or lung or with acute infective endocarditis or infection of IV catheters. Treatment is high dose flucloxacillin or vancomycin. Uncomplicated staphylococcal aureus bacteremia should be treated for 14 days to reduce the risk of metastatic infection.
- Severe cellulitis, bites and necrotising fascitis accompanied by septicemia should be treated with optimum cover for Lancefield Group A *Streptococcus*, anaerobes, and coliforms. Treatment is piperacillin tazobactam + clindamycin/(meropenem + clindamycin)
- Septicemia in patients rendered neutropenic by cytotoxic drugs involves coliforms and *Pseudomonas* sp. translocating to circulation directly from the bowel, while coagulase negative staphylococci also commonly arise from central venous catheter infection, Treatment is piperacillin tazobactam plus vancomycin.
- Staphylococcal toxic shock syndrome occurs in healthy women using vaginal tampons, in abortion or childbirth and occasional with skin and soft tissue infection and after packing body cavities such as nose. Flucloxacillin is used and elimination of the source by removal of tampon and drainage of the abscesses is also important.

ANTIMICROBIALS FOR SYSTEMIC THERAPY

Benzyl penicillin—is highly active against *Streptococcus pneumoniae* and *Streptococcus pyogenes*, *Strepto. viridans*, and enetrococci. For endocarditis, penicillin should be combined with gentamycin. Benzylpenicillin is the drug of choice for infections due to *Neisseria meningitidis* (meningococci meningitis and septicemia), *Bacillus anthracis*, *Clostridium perfringes* and *Tetani leptospira* and for *Borrelia burdorferi* (lyme disease in children). Benzylpenicillin may be given IM or IV (by bolus injection or by continuous infusion), For a sensitive infection–benzylpenicillin 600 mg 6 hourly.

- **Ticarcillin** is a carboxypenicillin used in combination with clavulanic acid to provide greater activity against β-lactamase producing organisms. It is given IM or slow IV injection or by rapid IV infusion 3.2 g 6 hourly IV.
- For *Pseudomonas septicemia*, a ureidopenicillin (piperacillin) plus an aminoglycoside provide a synergistic effect (coadministration in the same fluid results in inactivation).
- **Imipenem** combined with cisplatin to protect it from cleavage by dihydropeptidase found in brush border of the proximal renal tubule. Imipenem is used to treat septicemia, intra-abdominal infections and nosocomial pneumonia. High levels of imipenem evoke seizures. The dose is 1–2 g/day by IV infusion in 3–4 doses.
- **Meropenem**—is stable to dihydropeptidase and can be given without cisplatin. It reaches therapeutic levels in bacterial meningitis without inflammation. Dose: 500 mg 8 hourly IV.
- **Ertapenem:** Is given as single daily injection for multiresistant Gram-negative bacteria such as extended spectrum β-lactamases (ESBL) producing coliforms. Dose: 1 g, once daily, IV/IM for 7 days.
- **Vancomycin**—is a glycopeptide and acts on aerobic and anaerobic gram +ve bacteria, including MRSA, methicillin resistant *Staphylococcus epidermidis*, *Enterococcus* species and *C. difficile*. It inhibits cell wall formation at a site different from β-lactam antibacterials. It may be given IV for enterococcal endocarditis in patients who are allergic to benzylpenicillin 1 g 12 hourly infused IV over 1 hr. Adverse effects are nephrotoxicity, hypotension and hypersensitivity on IV inj.
- **Teicoplanin**—is active against gram-positive bacteria and half-life ($t_{1/2}$) is 50 hours once daily IV or IM for 3–4 days. 400 mg 1st day, then 200 mg/day IV/IM.
- **Daptomycin**—is bactericidal concentration dependent, lipopeptide antibiotic produced by the bacterium *Streptomyces roseosporus* which was first isolated from soil sample. It has activity against vancomycin resistant enterococci, bacteremia caused by S. aureus. and MRSA. It is administered by single daily injection. Dose—4 mg/kg every 24 hrs for 7 days.
- **Sodium fusidate**—is a valuable drug for treating serious staphylococcal infections including osteomyelitis and is available as IV and oral preparations. Dose—500 mg IV 8 hrly.
- **Linezolid**—is used against Gram +ve organisms including resistant isolates like MRSA, vancomycin-resistant enterococci (VRE), penicillin resistant enterococci. It can cause gastrointestinal upset, nausea, diarrhoea, headache, and rash. The dose is 600 mg IV infusion.
- **Quinupristin dalfopristin**—is a 30–70% combination of two streptogramin molecules in a ratio of 30 to 70, respectively. They synergically inhibit protein synthesis and are bactericidal and have long postantibiotic effect, active against Gram +ve coccus, vancomycin resistant *Enterococcus faecium*. The dose is 7.5 mg/kg every 8 hrs.

- **Tigecycline** is a tetracycline and exhibits broad spectrum activity against MRSA, multidrug resistant streptococci, vancomycin resistant enterococci, ESBL producing gram –ve bacteria, *Acinobacter baumannii* and many anaerobes. It is used to treat complicated skin and soft tissue infections, complicated intra-abdominal infections and community acquired pneumonia. 100 mg dose followed by 50 mg twice daily by IV infusion over 1 hour. No dose adjustment is required in renal failure and a dose reduction is required in hepatic failure.

Meningitis in ages above 5 years is caused by *Neisseria meningitidis* and *Streptococcus penumoniae*. Treat with benzylpenicillin 2.4 g 4 hourly. In case of *Neisseria meningitidis* add rifamipicin for 2 days prior to discharge from hospital. Optimum therapy for known penicillin-resistant pneumococcal meningitis comprise ceftriaxone 2 g IV 12 hourly plus vancomycin IV 15 mg/kg 12 hourly plus rifampicin 300 mg IV 12 hourly.

Children under 5 years, Neisseria meningitis is now the commonest pathogen and Hemphilus influenzae less isolated. Give ceftriaxone.

- In neonates, give cefotaxine or ceftazidime plus gentamycin. For group B streptococci, give benzyl penicillin plus gentamycin. Dexamethasone given IV (0.15 mg/kg 6 hourly for 4 days and early appears to reduce long term neurological sequelae.

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Chapter 48

Treatment of Osteoporosis

The bone mass normally thicknes up to the age of 30 years after which it gradually and progressively declines, faster in women than in men. Osteoporosis is caused due to several factors in which there is decrease in quantity of trabecular and cortical bone mass, leading to increased frequency of fractures. **Postmenopausal osteoporosios is very common in women** and senile type in older women.

A. The dietary modification advised in the treatment of osteoporosis are reduction in common salt consumption as Ca is co-excreted with sodium in increased quantities in urine. Also Animal foods restriction advised. Restriction on alcohol and smoking is necessary.

B. Exercise recommended is walking and resistant exercise, weight lifting using moderate weights.

C. **Pharmacotherapy:** Alendronate, risedronate and raloxifene have been used to increase BMD (bone mass density) and decrease the incidence of fractures. The use of HRT is preferred in elderly menopausal women with menopause symptoms whereas SERM (raloxifene) may be preferred in middle or late post-menopausal. Discussing individual drugs used in the treatment of osteoporosis:

Calcium: A daily calcium intake of 1200–1500 mg together with vitamin D of 800 IU/day and regular physical exercise are recommended to build up starting bone mass.

Vitamin D: It usually contains D_2 (ergocalciferol) and D_3 (cholecalciferol). Cholecalciferol is a pure vitamin D_3 obtained from UV irradiation of 7-dehydrocholesterol. Ergocalciferol (D_2) is obtained by UV irradiation of ergosterol from yeast and fungi. The metabolite 1,25-(dihydroxycholecalciferol (calcitriol), the active form of D_3 stimulates the intestinal absorption of calcium and phosphate. Deficiency of vitamin D occurs when the dietary calcium supply is low or when the physiological demands are increased as during growth or lactation. Vitamin D is available in the market in many formulations as multivitamin preparations, in fish liver oils, in combination with calcium salts and as vitamin D preparations alone. Calciferol (vitamin D_2)—50,000 U capsules, cholecalciferol inj (vitamin D_3) as oily sol for IM, inj. calcitriol sachet—60, 000 IU suspended in milk/water available.

Biphosphonates: They are given orally and are poorly absorbed. They are characterized by P-C-P bonds similar to nature of native pyrophosphate P-O-P found in bony hydroxyapatite. Their potency varies depending upon their length and structure of the

side chain. They bind to hydroxyapatite crystal of bone and inhibit the dissolution of bone crystal. They reduce the recruitment and inhibit the activity of osteoclasts activity increasing their apoptosis. When given orally their bioavailability is low.

Alendronate and Risedronate are used along with calcium and vitamin D. They reduce the incidence of vertebral and hip fractures. Alendronate 70 mg given once a week is as effective and safe as daily administration. The patient should be instructed to take the drug on empty stomach in the morning with 250 ml of water, in erect posture (not to lie down at least ½ an hour and not to eat or drink anything except water for a shorter period).

Zoledronate: It is bisphosphonate, 4 mg diluted in 100 ml saline, infused IV once every year is used for osteoporosis in post-menopausal Women.

Raloxifene: It is selective estrogen receptor modulator (SERM) with beneficial effects on bone and CVS. It causes dose dependent increase in osteoblastic activity and decrease in osteoclastic activity. It undergoes high first pass metabolism and has low oral bioavailability. It is used in dose of 60 mg once daily in prevention of menopausal osteoporosis. Its adverse effects include hot flushes, leg cramps and thrombo-embolic disease.

Intranasal salmon calcitonin: It is secreted by C cells in thyroid follicles. The synthetic hormone administered in the dose of (200 IU) per activation. It more effectively prevents cancellous bone marrow loss than cortical bone marrow loss in postmenopausal women. It is more potent than human calcitonin because of its high affinity for the human calcitonin receptor and its slow metabolic clearance. It is given by SC or IM or by nasal spray.

Parathyroid hormone (Teriparatide): 20 µg once daily SC, PTH 1–34 has been shown to increase BMD as well as bone mass and strength by stimulating endosteal and periosteal bone formation with anabolic action on bone.

Estrogen replacement therapy: At the onset of menopause, ERT alone with calcium supplementation and vitamin D_3 are standard treatment for treating osteoporosis. The treatment with estrogens should be started shortly after the onset of menopause and may need to be continued for life. The benefits of ERT include increased bone density, decreased vaginal atrophy but long-term use also carries a risk of developing breast cancers, endometrial cancers, stroke and deep vein thrombosis. To prevent the adverse effects of estrogens, a sequential regimen is used giving (0.625 mg/day) conjugated estrogens or 25–50 ug/day of ethinyl estradiol daily with 5–10 mg of medroxyprogesterone acetate added on days 14–21 of the cycle.

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Chapter
49

Treatment of Common Ophthalmic Diseases

INFECTIVE CONJUNCTIVITIS

ACUTE BACTERIAL CONJUNCTIVITIS

(*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pneumococcus*, *Streptococcus pyogenes*, *Neisseria*) (Fig. 49.1a).

CLINICAL DIAGNOSIS

- Discomfort, foreign body, grittiness
- Blurring and sudden onset redness
- Mild photophobia
- Conjunctival congestion
- Mucopurulent discharge
- Lid margins glued together
- Coloured halos
- Flakes of mucopus
- Chemosis

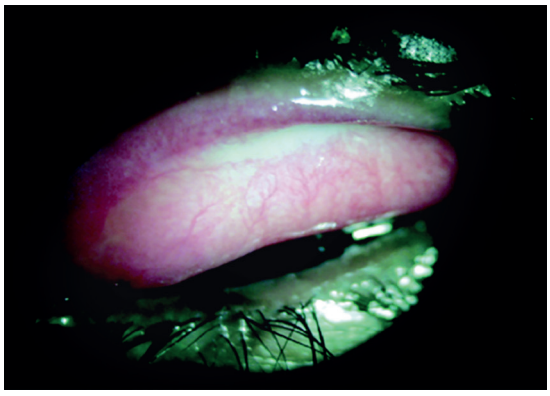

Fig. 49.1a: Bacterial conjunctivitis (*Image courtesy:* Ophthalmology OPD, AIIMS, Rishikesh)

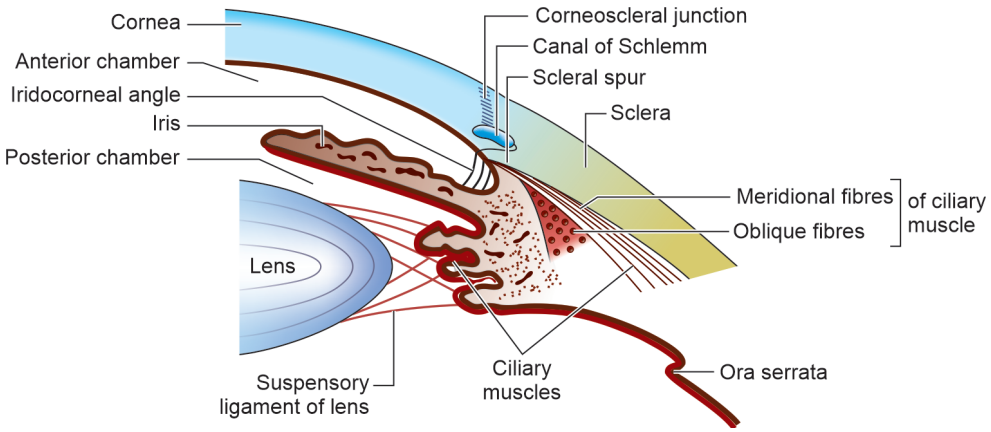

Fig. 49.1: Eye structure and aqueous flow

Treatment

Topical eyedrops/ointment 3–4 hourly in a day

- Gentamicin (0.3%)
- Chloramphenicol (1%)
- Tobramycin (0.3%)
- Framycetin (0.3%)
- Irrigation of conjunctival sac with sterile luke warm water.

CHLAMYDIAL CONJUNCTIVITIS/TRACHOMA

CLINICAL DIAGNOSIS

- Mild foreign body sensation
- Congestion of upper tarsal and conjunctiva
- Follicles (sago-grains) visible on the upper tarsal, conjunctiva, and fornix
- Papillae
- Superficial keratitis
- Herbert follicles in limbal area
- Progressive pannus
- Arlt's line—conjunctival scarring

Treatment

- Tetracycline (l%) or erythromycin (1%) eye ointment × 6 weeks
- Sulfacetamide (20%) eye drops TDS.
- Tab tetracycline or erythromycin 250 mg QID × 4 weeks
- Tab doxycycline 100 mg BD × 4 weeks
- Azithromycin 20 mg/kg, single dose
- Permanent lash removal
- Lubricating drops
- Penetrating keratoplasty

ADENOVIRAL CONJUNCTIVITIS

CLINICAL DIAGNOSIS

- Watery discharge
- Chemosis
- Preauricular lymph nodes
- Moderate congestion
- Follicles
- Corneal involvement

Treatment

- Sunglasses and cold compresses
- Eyedrops that decongest and lubricate
- Topical antibiotics
- No steroids
- **Preventive measures:** Handwashing, no eye rubbing/common use of towel or handkerchief

HERPETIC CONJUNCTIVITIS

CLINICAL DIAGNOSIS

- Vesicular lesions of face and lids
- Moderate congestion
- Follicles
- Corneal involvement: rarely
- Watery discharge
- Chemosis
- Preauricular lymph nodes

Treatment

- Topical antiviral drugs, e.g. aciclovir
- Supportive measures.

ALLERGIC CONJUNCTIVITIS

SIMPLE ALLERGIC/IGE MEDIATED

Clinical Diagnosis

- Itching
- Watery, stringy discharge
- Hyperemia
- Papillae
- Lid edema

VERNAL KERATOCONJUNCTIVITIS (VKC) OR SPRING CATARRH/TYPE 1 (Fig. 49.2)

Clinical Diagnosis

- Marked burning, itching
- Ropy discharge
- Photophobia
- Lacrimation
- Cobblestone papillae on upper tarsal conjunctiva
- Horner Trantas spots at limbus
- Shield ulcer on cornea

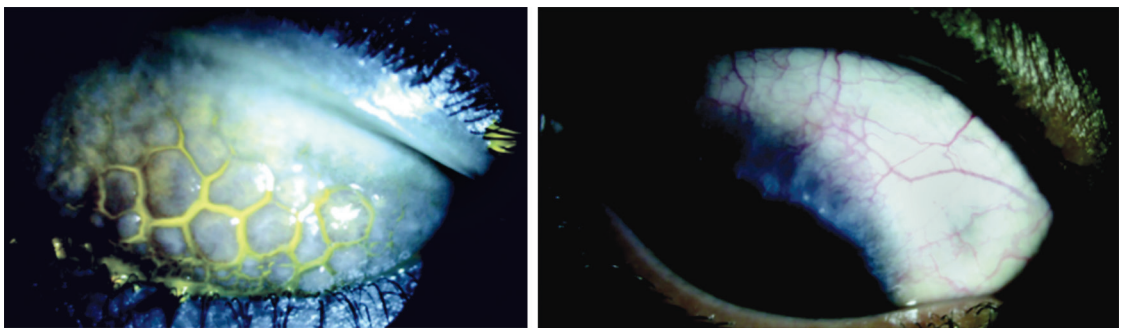

Fig. 49.2: Vernal keratoconjunctivitis (*Image courtesy:* Ophthalmology OPD, AIIMS, Rishikesh)

ATOPIC KERATOCONJUNCTIVITIS/TYPE I, IV MEDIATED

Clinical Diagnosis

- Itching
- Photophobia
- Blepharitis
- Congestion of conjunctiva
- Mucoid discharge
- Dennie morgan folds (eye folds)
- Trichiasis
- Corneal involvement

GIANT PAPILLARY CONJUNCTIVITIS (GPC)/MECHANICALLY-INDUCED

Clinical Diagnosis

- Itching
- Stringy discharge
- Fluctuation of mucous discharge
- Considerable deposits of contact lens protein
- Overly mobile contact lens due to upper lid capture
- Hyperaemia and papillae of the superior tarsal
- Whitish scarring and focal apical ulceration
- Ptosis

PHLYCTENULAR KERATOCONJUNCTIVITIS/TYPE IV

Clinical Diagnosis

- Irritation
- Watering
- Phlycten (nodule on bulbar conjunctiva near limbus)
- Nodule ulceration at apex
- Necrosis and ulceration in a large phlycten causing a severe pustular conjunctivitis

Treatment

- Avoiding allergen
- Cold compresses
- Dark goggles
- Artificial tears
- Discontinuation of contact lens (GPC)
- Topical vasoconstrictors
- Mast cell stabilizers—cromoglycate sodium
- Olopatadine eyedrops 0.1% solution
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Topical steroids (oral in advanced cases of VKC)
- Systemic antihistaminics

CORNEAL ULCER

Bacterial corneal ulcer (Staphylococci, *Pseudomonas, Streptococcus pneumoniae,* Enterobacteriaceae *and Neisseria)*	**Fungal corneal ulcer** *(Aspergillus, Fusarium, Candida)*
Clinical diagnosis	
• Pain, foreign body sensation • Redness • Blurred vision • Photophobia • Watering • Sterile hypopyon • Blepharospasm, chemosed conjunctiva, • Corneal ulcer-epithelial defect with swollen, over hanging margins, floor covered by necrotic material, with surrounding edema • Investigation: Corneal scraping (Gram, Giemsa stain, aerobic C/S)	• Less symptoms (similar to bacterial) • More signs: The edges of the corneal ulcer are rolled and appear dry • Pigmented ulcer • Feathery margins, sterile immune ring • Satellite lesions • Hypopyon unsterile • Endothelial plaque • Investigation: Corneal scraping (KOH, SDA, fungal C/S)

Treatment of bacterial ulcer	***Treatment of fungal ulcer***
• Topical antibiotics: Fortified vancomycin 5%, fortified tobramycin 1.3%	• Topical antifungals: Eyedrops natamycin 5%, fluconazole (0.2%)
• Cycloplegics: 1% atropins	• Systemic antifungals
• NSAIDs	• General measures
• Vitamines B and C	• Keratoplasty
• Dark goggles, hot fomentation	
• Antiglaucoma medications	
• Bandage contact lens, tissue adhesive glue	
• Keratoplasty	

VIRAL CORNEAL ULCER: HERPES AND ACANTHAMOEBA (Fig. 49.3)

Herpes	***Acanthamoeba***
Clinical diagnosis	
• Systemic features—fever, malaise • Vesicular skin lesions • Ocular redness, photophobia, blurring of vision • Dendritic ulcer • Geographical ulcer • Decreased corneal sensations (herpes simplex, herpes zoster)	• Marked pain • Redness • Photophobia • Radial keratoneuritis • Epithelial pseudodendrites • Limbitis with diffuse or focal anterior stromal infiltrates • Perineural infiltrates • Scleritis • Corneal melting

Treatment (herpes)	*Treatment Acanthamoeba*
• Topical—acyclovir 3%, ganciclovir 0.15% 5 times a day	• General measures
• Systemic antiviral—acyclovir 400 mg (herpes), 800 mg (zoster), famciclovir 250 mg, bd	• Topical antiamoebic agents
• General measures	• **Diamidines:** Propamidine isethionate (0.1%), and hexamidine (0.1%)
• Keratoplasty	• **Biguanides:** Polyhexamethylene biguanide (PHMB), 0.02% and chlorhexidine, 0.02%
	• Aminoglycosides *Multiple drug therapy* is needed for a long time

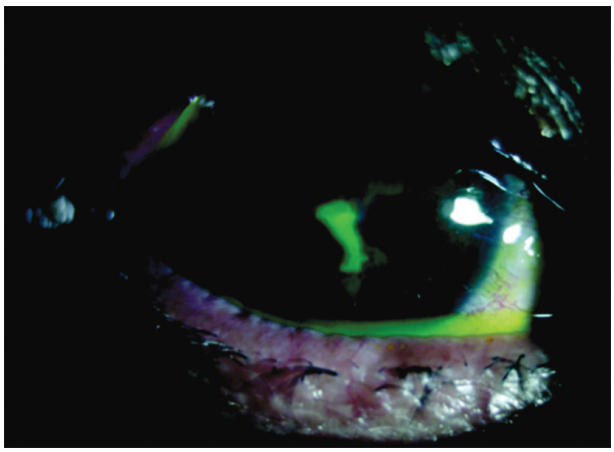

Fig. 49.3: Viral corneal ulcer (*Image courtesy*: Ophthalmology OPD, AIIMS, Rishikesh)

LID DISORDERS

Internal hordeolum	*Chalazion*	*External hordeolum/Stye*
Suppurative inflammation of meibomian gland	Chronic non-infective granulomatous inflammation of meibomian gland)	Acute suppurative inflammation of gland of Zeis/Moll

Clinical diagnosis	*Clinical diagnosis*	*Clinical diagnosis*
• Pain associated with lid swelling	• Painless swelling in eyelid	• Sudden pain accompanied by eyelid swelling, slight watering and photophobia
• Watering	• Heaviness in lid	• Tender swelling at lid margin associated with pus point on eyelash
• Photophobia	• Non-tender, firm nodule away from lid margin	
• Firm, tender swelling of lid with edema with pus points on tarsal conjunctiva		

Treatment

Internal hordeolum	*Chalazion*	*External hordeolum*
Hot compresses, tds	Conservative treatment	Incision and curettage
Topical antibiotics tds	Intralesional injection of triamcinolone	Diathermy
NSAIDs	Incision and curettage	Oral tetracyclines
Systemic antibiotics	Diathermy	
Surgical incision	Oral tetracyclines	

Glaucoma—is not a single disease process, but rather a group of disorders identified by a progressive optic neuropathy that causes a distinctive appearance of the optic disc and a particular pattern of irreversible visual field defects that are frequently but not always linked to elevated intraocular pressure (IOP). IOP is therefore the most important risk factor for the development of glaucoma, though it is not the only risk factor.

ANGLE CLOSURE GLAUCOMA

Clinical Features

1. Headache, brow ache
2. Pain
3. Nausea, vomiting
4. Temporary unilateral blurred vision
5. Light surrounded by colored halos.

Signs (Fig. 49.4)

1. Conjunctiva is chemosed, and congested.
2. Cornea is hazy.
3. The anterior chamber may have aqueous flare or cells.
4. As seen on gonioscopy, the anterior chamber angle is totally closed.
5. A discoloured iris may be seen
6. The pupil is fixed, vertically oval, and mid-dilated.
7. IOP is significantly increased, typically between 40 and 60 mm Hg
8. Oedematous and hyperaemic optic disc
9. Latent angle closure glaucoma in the fellow eye is indicated by a small angle and a shallow anterior chamber.

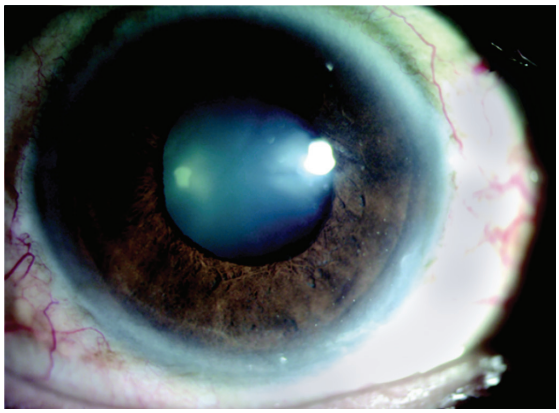

Fig. 49.4: Closed angle glaucoma showing fixed dilated pupil (*Image courtesy:* Ophthalmology OPD, AIIMS, Rishikesh)

TREATMENT OF ANGLE CLOSURE GLAUCOMA

Medical Therapy

1. Beta-blockers (e.g. timolol maleate 0.5%) block β_2-receptors in ciliary epithelium and reduce ocular blood flow/reduce aqueous formation
2. Prostaglandin analogs (e.g. latanoprost 0.005%) increase uveoscleral outflow

3. Carbonic anhydrase inhibitors (e.g. dorzolamide, 2%) reduce generation of bicarbnate in the ciliary epithelium, reduce aqueous formation
4. Adrenergic agonists (e.g. brimonidine 0.2%) dipivefrine 0.1%, apraclonidine 0.5%, decrease aqueous section by α_2-action in ciliary body.

Surgical

1. Argon laser trabeculoplasty (ALT)
2. Trabeculectomy
3. Glaucoma filtration devices.

DIAGNOSIS

1. Clinical diagnosis, distinguish among various causes of eye redness.
2. **Gonioscopy:** Closed angles

PRIMARY OPEN ANGLE GLAUCOMA

Clinical Features

- Mild headache and eye ache.
- Occasionally, an observant patient may notice a defect in the visual field.
- Regular changes of presbyopia spectacles.
- Patients experience delayed dark adaptation.

Signs (Fig. 49.5)

1. IOP above 21 mm of Hg
2. Optic disc changes, cup disc ratio more than 0.6:1
3. Visual field defects.

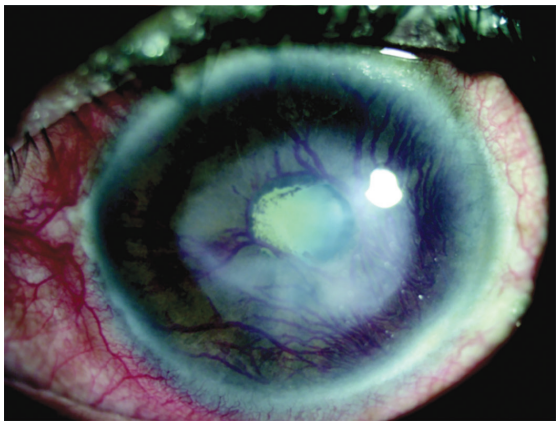

Fig. 49.5: Open angle neovascular glaucoma (*Image courtesy:* Ophthalmology OPD, AIIMS, Rishikesh)

DIAGNOSIS

1. Tonometry
2. Gonioscopy (examination of angle structures)
3. Documentation of optic disc changes.
4. Slit-lamp examination.
5. Perimetry to detect the visual field defects.

MEDICAL MANAGEMENT OF OPEN ANGLE GLAUCOMA

1. Intravenous mannitol (1 g/kg body weight), a systemic hyperosmotic drug, should be administered immediately to decrease IOP.
2. Acetazolamide (a carbonic anhydrase inhibitor) should be administered as a 500 mg intravenous injection followed by 250 mg tablet three times daily.
3. As needed, analgesics and antiemetics.

4. Pilocarpine 2% eyedrops should be started when hyperosmotic drugs have decreased the IOP. Physostigmine as 0.1% miotic increases the tone of ciliary muscle and sphincter pupillae which pull on and improve alignment of trabeculae to increase outflow of aqueous humour, in open angle glaucoma.
5. β-blockers (e.g. timolol maleate 0.5%)
6. Corticosteroid eyedrops to reduce inflammation.

SURGICAL MANAGEMENT

1. Peripheral iridectomy (PI)
2. Filtration surgery
3. Clear lens extraction
4. Prophylactic treatment in fellow eye (preferably PI).

ANTERIOR UVEITIS

Symptoms

1. Pain
2. Redness
3. Photophobia
4. Lacrimation
5. Defective vision

Signs (Fig. 49.6)

1. **Conjunctiva**: Circumcorneal congestion
2. **Cornea:** Keratic precipitates, corneal oedema
3. **Anterior chamber:** Cells and flare, hypopyon
4. Change in iris colour, pattern, iris nodules, posterior synechiae
5. Pupil irregular in shape
6. **Lens:** Pigments over anterior capsule, complicated cataract
7. **Angle:** Secondary glaucoma
8. **Vitreous:** May show cells.

DIAGNOSIS

1. Hematological investigations
   TLC and DLC to have general understanding about the body's inflammatory reaction
   ESR to determine if the body has any chronic inflammatory conditions
2. Serological examination including syphilis, toxoplasmosis, and histoplasmosis.
3. Rh-factor and antinuclear antibody tests.
4. Radiological studies include chest, lumbar spine, sacroiliac joint, and paranasal sinus X-rays.
5. Skin tests. The tuberculin test is one of them.

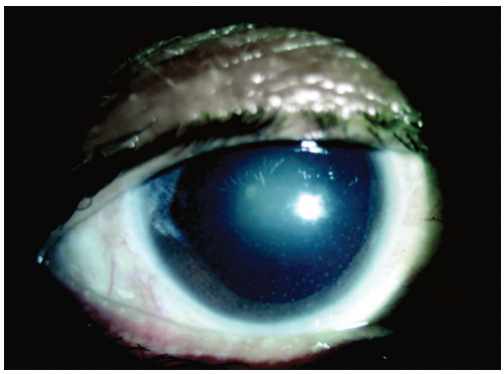

Fig. 49.6: Anterior uveitis (*Image courtesy:* Ophthalmology OPD: AIIMS, Rishikesh)

Treatment

1. **Topical**
   - Cycloplegics (e.g. atropine sulfate 1%)
   - Steroids
2. **Systemic drugs**
   - Steroids
   - NSAIDs
   - Immunosuppressives
3. **Treatment of specific etiology**

TRAUMA OF EYE

Symptoms	*Investigations*
1. History of injury (blunt penetrating trauma)	1. Visual acuity
2. Sudden painful diminution of vision	2. Slit-lamp examination
3. Redness	3. X-ray orbit (AP and lateral) to rule out intraocular foreign body)
4. Photophobia	
5. Decimation	

Signs of trauma and treatment	
Signs	*Treatment*
1. **Conjunctiva:** Circumcorneal congestion 2. **Cornea:** Abrasion, erosions, tears, blood staining 3. **Sclera:** Tear 4. **Anterior chamber:** Hyphema 5. **Iris:** Tear, traumatic mydriasis, iridodialysis, angle recession 6. **Lens:** Vossius ring pigments on anterior capsule, traumatic cataract, subluxation 7. **Vitreous:** Hemorrhage 8. **Choroid:** Rupture 9. **Retina:** Berlin's ed ema, tears, hemorrhage, retinal detachment. 10. Pupil mydriasis (Fig. 49.7)	1. Primary repair in corneal/scleral lacerations. 2. Removal of intra-ocular foreign body 3. Intravitreal antibiotics 4. Vitrectomy (in intraocular FB/retinal detachment)

Atropine, homatropine, cyclopentolate, tropicamide are mydriatics (dilate the pupil) used in refraction testing/iritis/uveitis/fundoscopic examination.

Characteristic Drug Administration Routes

Eye is often regarded as the exteriorization of brain. Pharmacokinetic properties of eye are governed similar to brain in the form of blood aqueous barrier and blood retinal barrier (akin to blood—brain barrier).

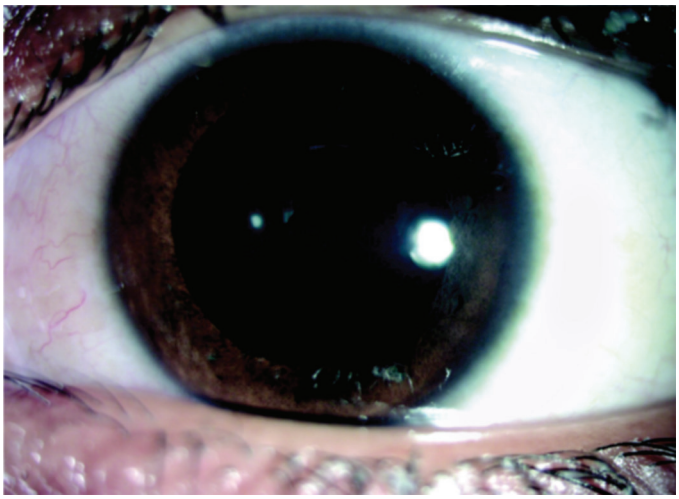

Fig. 49.7: Traumatic mydriasis (*Image courtesy:* Ophthalmology OPD, AIIMS, Rishikesh)

These lipoidal barriers allow passage of only drugs of low molecular weight (generally below 500 daltons), high lipophilicity and low ionic charges. Similarly, the pharmacodynamic potential of a drug is governed by the unique anatomical ocular design. The tight junction of corneal epithelium disallows permeation of a multitude of drug molecules. Similarly, the continuous permeation of ocular cul de sac by a stream of tears dilutes drug concentration of eye drops and negates their efficacy.

Internally, the tight adhesion of the retinal pigmentary epithelium with the Bruchs membrane of choroid disallows free exchange of molecules from the inner vitreous to the middle coat of eye.

Drug administration for ocular conditions must take cognizance of these factors to ensure adequate drug bioavailability and efficacy.

Popular route of drug administration remains in the form of eyedrops.

Not only it is convenient but also effective non-invasive form of drug delivery that can be employed frequently to ensure adequate concentration. Eye ointments, drug impregnated contact lenses and drug implants (ocuserts) are seperate modalities of drug administration that ensure a continued drug delivery.

Invasive techniques ranging from subconjunctival, subtenons, intracameral and intravitreal injections are reserved for situations that warrant a high concentration at the localised site or when bypassing the ocular barriers become necessary in treatment.

It is noteworthy that the route of drug administration and not just the drug efficacy spells the difference between cure and failure.

Treatment of Macular Edema and Neovascularisation

To ensure vision, the ocular structures in line with the visual axis are kept transparent. These include the cornea, human crystalline lens and the retina. Of the many physical factors that ensure transparency, maintaining a continued dehydrated state is a mandatory requirement for vision. This is achieved through different anatomical and physiological means.

The macula lutea which is the visually most sensitive part of the retina lies at the posterior pole of the eye. It is enriched by a high concentration of photoreceptors mainly the cones and

also the rods. Fluid accumulation at the macula is generally an after math of disturbance in the inner blood–retinal barrier.

It is a sequential effect of either a physical insult or a pathologic under-way. Macular edema is a common aftermath of retinopathy particularly diabetic retinopathy. Coexisting with macular edema are the challenges of neovascularisation which are the signature tones of retinal hypoxia.

Conventionally macular edema and neovascularisation had been managed with laser or corticosteroid.

Physical properties of laser that included photocoagulation and a focal burn production was exploited to minimise edema and seal the leaking vessels. This was particularly effective in conjunction with the investigative procedure of fundus fluorescein angiography. However, its role largely remained restricted to prophylaxis. Intravitreal corticosteroids had the limitation of a short half-life in the given concentration and had a restricted role in managing macular edema and neovascularisation.

Lately prolonged steroid implant such as ozurdex has shown a more promising role but the technical nuances and cost factor has prohibited its general acceptability.

Last couple of decades have largely been occupied by the advent of anti vascular endothelial growth factor (VEGF) drugs that seem to be more efficacious in managing macular edema and neovascularisation resulting from a variety of retinopathies and vascular occlusions. While the first prototype of this class bevacizumab (avastin) that was developed to fight colon cancer gained FDA approval in year 2004 and was concomitantly shown effective in wet AMD (age related macular degeneration), its dose 1.25 mg to 2.5 mg. It's later congeners like Ranibizumab 0.5 mg, Aflibercept 2 mg have shown better acceptability and results. Lately the introduction of Broculizumab has effectively tackled the issue of repeated injections of anti VEGF at short intervals and improved the clinical outcome. While a detailed discussion on anti VEGF is beyond the scope of this text it needs to be highlighted that nearly a quarter of retinal diseases are tackled with anti VEGF therapy today. The injections are given in vitreous humour.

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Chapter
50

Treatment of Common Pediatric Diseases

INTRODUCTION

The application of pharmacology to pediatrics is challenging and warrants an in-depth knowledge. At the outset, it is important to mention that children are not miniature adults, Some drugs given to adults as over the counter (OTC) are not used in pediatric practice. We will now see the use of drugs in some common pediatric conditions.

ACUTE GASTROENTERITIS

Diarrheal disease is the second leading cause of death in children under five years old, and was responsible for the deaths of 370,000 children in 2019. It is defined as loose, watery and possibly more-frequent bowel movements. During an episode of diarrhea, water and electrolytes including sodium, chloride, potassium and bicarbonate are lost through liquid stools, vomit, sweat, urine and breathing.

Most common cause in children under 5 years is viral. This generally tends to run its own course and the only supportive care is warranted.

Causes of Pediatric Diseases

Table 50.1: Bacterial, viral and parasitic causes of pediatric diseases

Bacterial	***Viral***	***Parasitic***
Escherichia coli	Rotavirus	*Giardia lamblia*
Shigella	Human caliciviruses	*Cryptosporidium parvum*
Vibrio cholerae	Cytomegalovirus	*Entamoeba histolytica*
Salmonella	Coronaviruses	*Cyclospora cayetanensis*
Campylobacter	Picornaviruses	*Isospora belli*
	Astroviruses	
	Enteric adenoviruses	

Principles of management: Four major components

1. Hydrate the patient.
2. Adequate feeds
3. Oral zinc supplement

4. Early detection of danger signs and management of complications
5. Treatment of infection

Symptoms and Signs of Dehydration

Dizziness, headache, tiredness, dry mouth, lips and eyes, sunken eyes, thirstness, irritability, decreased skin turgor, oliguria (Fig. 50.1).

Rehydration

It can be done with ORS or acceptable home available fluids **where ORS is not available**. The amount to be given is determined on the degree of dehydration.

Treatment plan A: No dehydration.

The mother is advised when to come to hospital after explaining danger signs, e.g. diarrhea >3 days, increased frequency/volume of stools, repeated vomiting, increasing thirst, refusal to feed, fever or blood in stools.

Treatment plan B: Some dehydration

The treatment is done at a health centre/hospital. The goal is to provide fluids for daily requirements and replacement fluids for any deficit.

a. Daily fluid requirement:

Up to 10 kg = 100 ml/kg
10–20 kg = should add 50 ml/kg
>20 kg = should add 20 ml/kg

For example: Daily fluid requirement in a child weighing 15 kg will be 1250 ml. (100 ml × 10 kg = 1000 ml; 50 ml × 5 kg = 250 ml; total 1250 ml)

b. Deficit replacement or rehydration therapy:

75 ml/kg of ORS to be given over 4 hours.
If the child not accepting orally, a nasogastric tube maybe used.

Treatment plan C: Severe dehydration

Immediately IV fluids should be infused. Fluid of choice is Ringer's lactate (RL) with D5%. Breastfeeding and semisolid food are continued.

Age	*First give 30 ml/kg*	*Then give 70 ml/kg*
<12 months	In 1 hour 30 minutes	In 5 hours 21/2 hours
IV fuid therapy in severe dehydration		

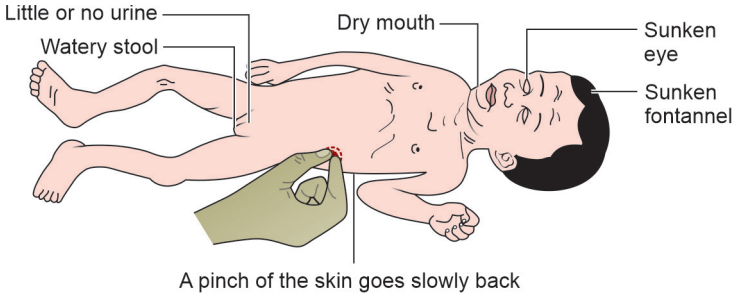


Fig. 50.1: Clinical signs of severe dehydration

In diarrhea, zinc deficiency causes reduced water and electrolyte absorption. Zinc supplementation reduces duration and severity of diarrhoea and prevents subsequent episodes, helping in recovery.

Zinc is recommended to be supplemented as sulfate, acetate or gluconate formulation.

Dose is 20 mg elemental zinc/day for children >6 months × 14 days.

Drug Therapy

Most episodes are self-resolving not needing any drug therapy, however, there are a few exceptions where acute diarrhea maybe a manifestation of a systemic illness. Antibiotics are thus warranted only in cases where sepsis is suspected.

Other agents are antisecretory, e.g. racecadotril and probiotics, e.g. *Lactobacillus, Bifidobacterium* and *Saccharomyces boulardii.*

Protein energy malnutrition: Severely malnourished child should be shielded against hypoglyce mia, hypothermia, electrolyte imbalance, deficiencies of iron, vitamins and other micronutrients. In children suffering from measles and severe protein energy malnutrition, should be given two doses of oral vitamin A-1 lac IU for <1 year and 2 lacs IU for >1 years. IV infusion of 5–10 ml/kg of 10% glucose solution is administered to prevent hypoglycemic deaths. Kangaroo skin mother care is given or blanket cover is given to prevent hypothermia. The caloric intake should not exceed 100 kcal/kg/day on the 1st day. After a week this can be increased to 150 kcal/kg/day and 2–3 g/kg/day of proteins. Total amount of fluids are to be taken within 100–125 ml/kg/day.

PNEUMONIA

It is an acute lower respiratory tract infection usually of a viral etiology in ~40% patients, e.g. by respiratory syncytial virus (RSV), influenza, parainfluenza, adenovirus. In two-thirds of patients, a bacterial etiology maybe identified. Since the beginning of the SARS-COV2 pandemic in 2020, the suspicion for this agent is high in each case of lower respiratory tract infections (LRTI).

Clinical Features

Onset maybe acute or insidious with high fever, tachypnea, dyspnea and grunting.

This is followed by flaring of nostrils and chest retractions with progression of disease if not treated in time (Fig. 50.2).

According to National ARI Control Programme, all children with cough should be assessed for rapid respiration and difficulty in breathing, cyanosis and difficulty in feeding. It is then classified and the treatment strategy is laid accordingly.

a. **No pneumonia:** Children with normal respiratory rate, no chest indrawing and feeding well is assessed to be having URTI and is managed symptomatically.
b. **Pneumonia:** If there is rapid breathing and chest indrawing but a normal oxygen saturation and is feeding well, can be managed on OPD basis with amoxycillin (40 mg/kg/dose twice daily × 5 days)

   The danger signs are explained to caretakers and need for admission is emphasized if condition worsens.
c. **Severe and very severe pneumonia:** Severe chest indrawing with low oxygen saturation and presence of danger signs (lethargy, bluish discolouration, poor feeding or seizures).

Fig. 50.2: Chest retractions

These patients require admission and monitoring.

Treatment entails supportive care, e.g. O_2 support, fluids, antimicrobial therapy:

First-line: IV Ampicillin (50 mg/kg/6 hourly × 5 days) with IV gentamicin (5–7.5 mg/kg/day 8 hourly × 5 days)

Second-line: IV Ceftriaxone (50–75 mg/kg/day q12–24 hourly)

MEASLES

Is a common childhood viral exanthematous illness.

Immunisation has led to a remarkable decrease in mortality but the incidence remains high in our country.

It is caused by a mRNA virus belonging to the paramyxovirus family. It is spread via droplets. It is highly contagious.

Clinical Features

Measles is common in preschool children. Transplacental antibodies offer immunity up to 9 months after which it starts declining.

Incubation period: 10 days

Child is infective 3 days before appearance and 3 days after disappearance of rash.

Prodromal phase is characterized by fever, running of nose, redness of eyes and dry cough. Rash appears after 2–3 days. Usually, starts on the face and spreads to arms, chest, and legs. Rash is erythematous. It fades in about 10 days leaving behind brownish discoloration.

Diagnosis is Clinical (Fig. 50.3)

Management is supportive:

- Antipyretics—paracetamol (15 mg/kg/dose, q4–6 hourly; maximum 60 mg/kg/day)
- Adequate fluid intake
- Maintenance of hygiene
- Adequate caloric intake
- Humidification

Fig. 50.3: Clinical signs of measles

CHILDHOOD ASTHMA

It can be controlled but cannot be cured.

Goals of Therapy

1. Maintain pulmonary function to near normal
2. Maintain physical activity to near normal
3. To avoid night time cough or wheezing with minimal chronicity
4. To prevent recurrence
5. To prevent adverse effects of treatment.

Long-term Management

Effective long-term management of asthma involves:

1. To identify and eliminate exacerbating factors, avoid exposures
2. Drug therapy
3. To educate guardians about nature of disease and instruct steps to avoid acute exacerbation

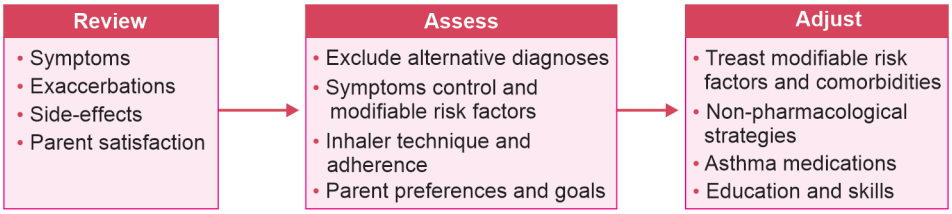
Principles of Pharmacotherapy

1. Assessment of components of severity
2. Assessment of risk factors causing aggravation.
3. Choice of drugs.
4. Chosing an appropriate inhalation device
5. Monitoring

Table 50.2: Probability of asthma diagnosis in children 5 years and younger		
Symptoms (cough, wheeze, heavy breathing) for <10 days during upper respiratory tract infections	Symptoms (cough, wheeze, heavy breathing) for >10 days during upper respiratory tract infections	Symptoms (cough, wheeze , heavy breathing) for >10 days during upper respiratory tract infections
2–3 episodes per year	>3 episodes per year, or severe episodes and/or night worsening	>3 episodes per year, or severe episodes and/or night worsening
No symptoms between episodes	Between episodes, child may have occasional cough, wheeze or heavy breathing	Between episodes, child has cough, wheeze or heavy breathing during play or when laughing
		Allergic sensitization, atopic, dermatitis, food allergy or family history of asthma
Few have asthma	Some have asthma	Most have asthma

Initiation of Therapy

Table 50.3: Personalized management of asthma in children 5 years and younger			
Step 1	***Step 2***	***Step 3***	***Step 4***
Consider intermittent short course inhaled corticosteroids (ICS) at onset of viral illness	Daily low dose ICS	Double low dose ICS	Continue controller and refer for specialist assessment
	Daily leukotriene receptor antagonist (LTRA) or intermittent short course of ICS at onset of respiratory illness	Low dose ICS + LTRA consider specialist referral	Add LTRA, or increase ICS frequency, or add intermittent ICS
As needed short-acting beta-agonist			
Infrequent viral wheezing and no or few interval symptoms	Symptoms pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. >/= 3 per year. Give diagnostics trial for 3 months. Consider specialist referral. Symptoms not well-controlled or >3 exacerbations per year.	Asthma diagnosis and asthma not well-controlled on low dose ICS	Asthma not well-controlled on double ICS
		Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures	



Selection of Appropriate Inhalation Device

a. Metered dose inhaler (MDI) (Fig. 50.4)

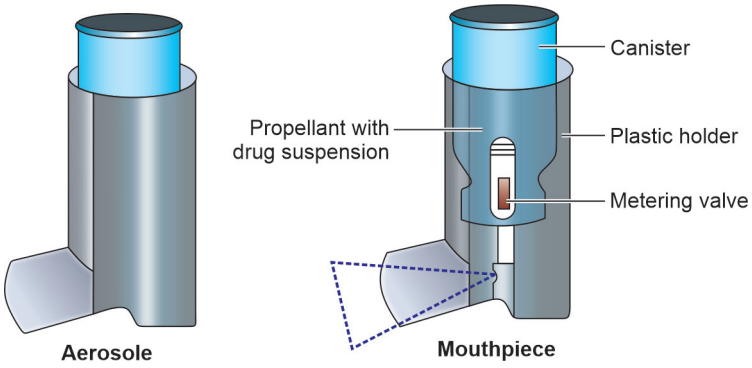


Fig. 50.4: Metered dose inhaler

b. MDI with spacer and face mask (Fig. 50.5)

c. **Dry powder inhaler:** Used >4 years of age (Fig. 50.6)

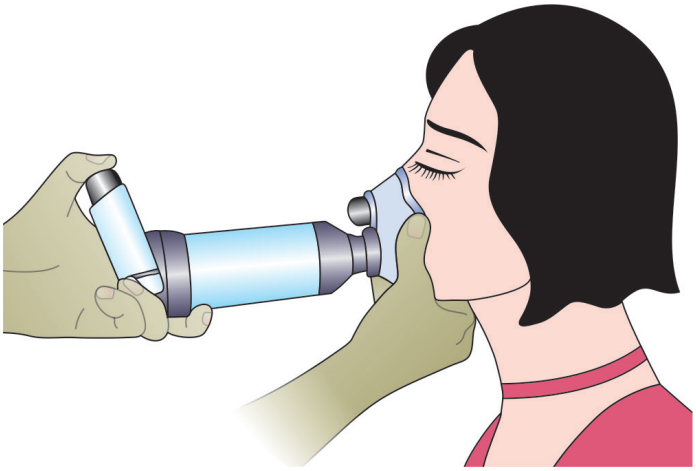


Fig. 50.5: Spacer with metered dose inhaler

Fig. 50.6: Rotahaler

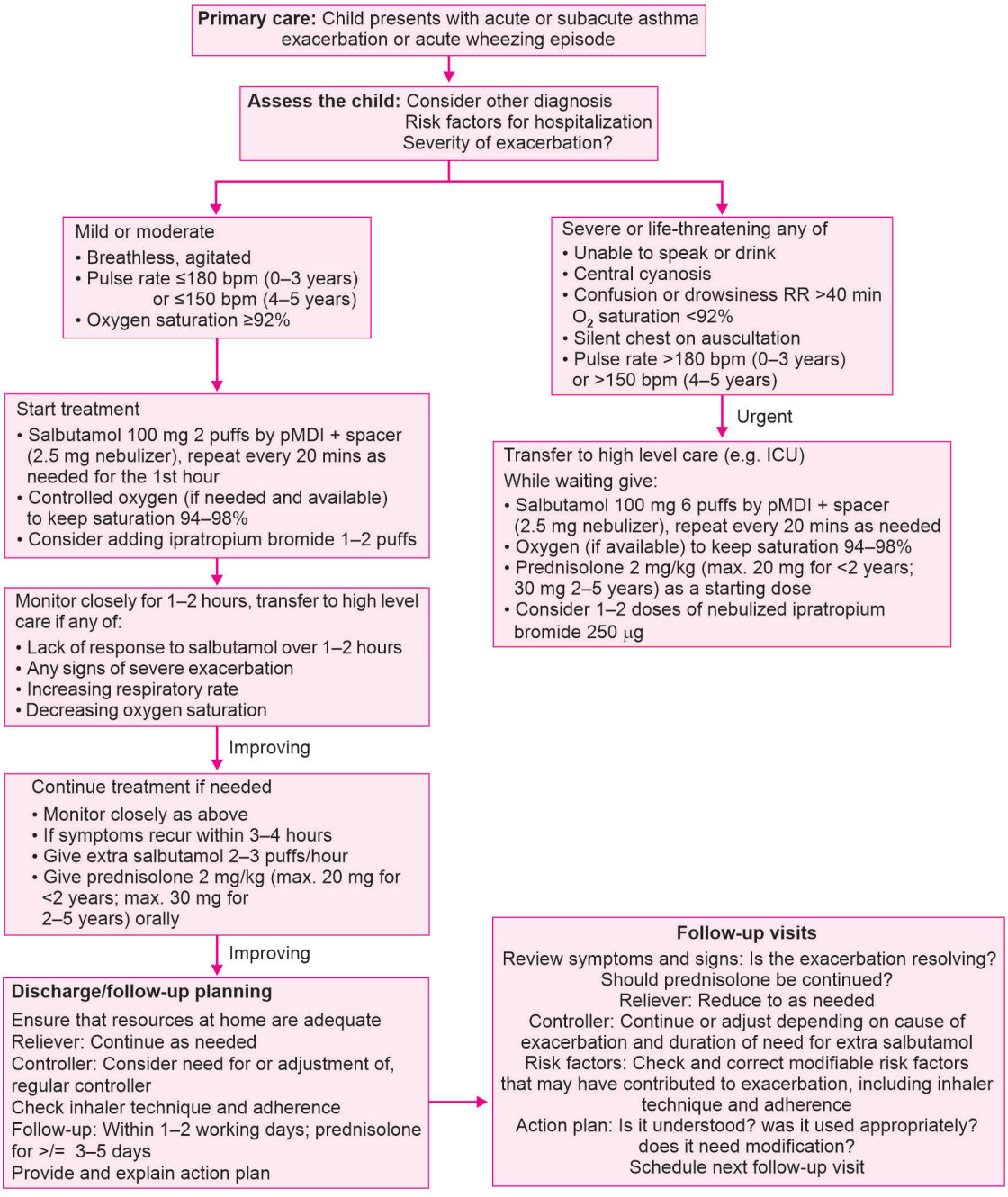

Primary care: Child presents with acute or subacute asthma exacerbation or acute wheezing episode
Assess the child: Consider other diagnosis
Risk factors for hospitalization
Severity of exacerbation?
Mild or moderate
• Breathless, agitated
• Pulse rate ≤180 bpm (0–3 years) or ≤150 bpm (4–5 years)
• Oxygen saturation ≥92%
Severe or life-threatening any of
• Unable to speak or drink
• Central cyanosis
• Confusion or drowsiness RR >40 min
O2 saturation <92%
• Silent chest on auscultation
• Pulse rate >180 bpm (0–3 years) or >150 bpm (4–5 years)
Urgent
Start treatment
• Salbutamol 100 mg 2 puffs by pMDI + spacer (2.5 mg nebulizer), repeat every 20 mins as needed for the 1st hour
• Controlled oxygen (if needed and available) to keep saturation 94–98%
• Consider adding ipratropium bromide 1–2 puffs
Transfer to high level care (e.g. ICU)
While waiting give:
• Salbutamol 100 mg 6 puffs by pMDI + spacer (2.5 mg nebulizer), repeat every 20 mins as needed
• Oxygen (if available) to keep saturation 94–98%
• Prednisolone 2 mg/kg (max. 20 mg for <2 years; 30 mg 2–5 years) as a starting dose
• Consider 1–2 doses of nebulized ipratropium bromide 250 μg
Monitor closely for 1–2 hours, transfer to high level care if any of:
• Lack of response to salbutamol over 1–2 hours
• Any signs of severe exacerbation
• Increasing respiratory rate
• Decreasing oxygen saturation
Improving
Continue treatment if needed
• Monitor closely as above
• If symptoms recur within 3–4 hours
• Give extra salbutamol 2–3 puffs/hour
• Give prednisolone 2 mg/kg (max. 20 mg for <2 years; max. 30 mg for 2–5 years) orally
Improving
Discharge/follow-up planning
Ensure that resources at home are adequate
Reliever: Continue as needed
Controller: Consider need for or adjustment of, regular controller
Check inhaler technique and adherence
Follow-up: Within 1–2 working days; prednisolone for >/= 3–5 days
Provide and explain action plan
Follow-up visits
Review symptoms and signs: Is the exacerbation resolving?
Should prednisolone be continued?
Reliever: Reduce to as needed
Controller: Continue or adjust depending on cause of exacerbation and duration of need for extra salbutamol
Risk factors: Check and correct modifiable risk factors that may have contributed to exacerbation, including inhaler technique and adherence
Action plan: Is it understood? was it used appropriately? does it need modification?
Schedule next follow-up visit

Fig. 50.7: Management of asthma

Acute Exacerbation of Asthma

Presence of any of the following would indicate life-threatening asthma:

- Bluish lips, skin, nails
- On auscultation no air sounds
- Poor breathing
- Fatigue/exhaustion
- Altered sensorium
- Peak expiratory flow rate (PEFR) <30% of predicted
- O_2 saturation <90%

Treatment to be Initiated

- Admit to PICU
- O_2 supplementation by mask/hood
- **Salbutamol inhalation:** To be repeated 3 times, 20 minutes apart
- Subcutaneous adrenaline (1:10,000 dilution) 0.1–0.3 ml
- IV Hydrocortisone 10 mg/kg

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Chapter
51

Treatment of Common Skin Diseases

The importance of dermatology cannot be overemphasized since sizeable percentage of total OPD visits comprise patients with dermatological ailments, hence this chapter is basically meant for all medical undergraduates to have an overview of the diseases and treatment of commonly seen dermatology OPD visits. The normal structure of skin is represented in Fig. 51.1.

Skin diseases can be classified broadly into:

1. Infective dermatoses—bacterial, viral and fungal infections
2. Inflammatory dermatoses
3. Genetic diseases

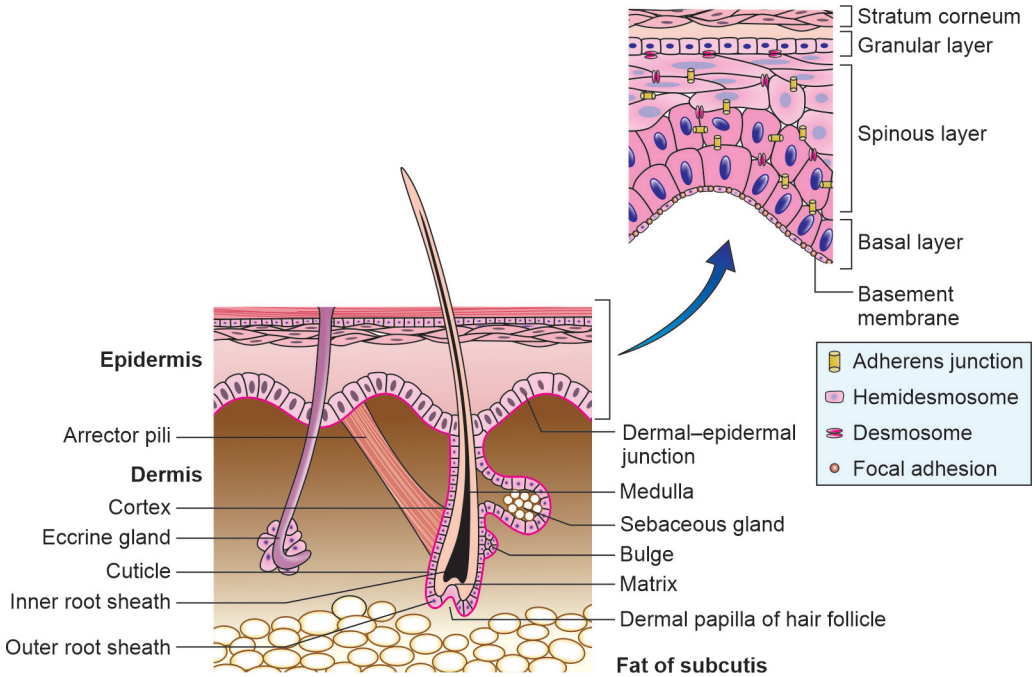


Fig. 51.1: Compartment of skin

INFECTIONS

Viral infections.

1. Warts (Verruca)

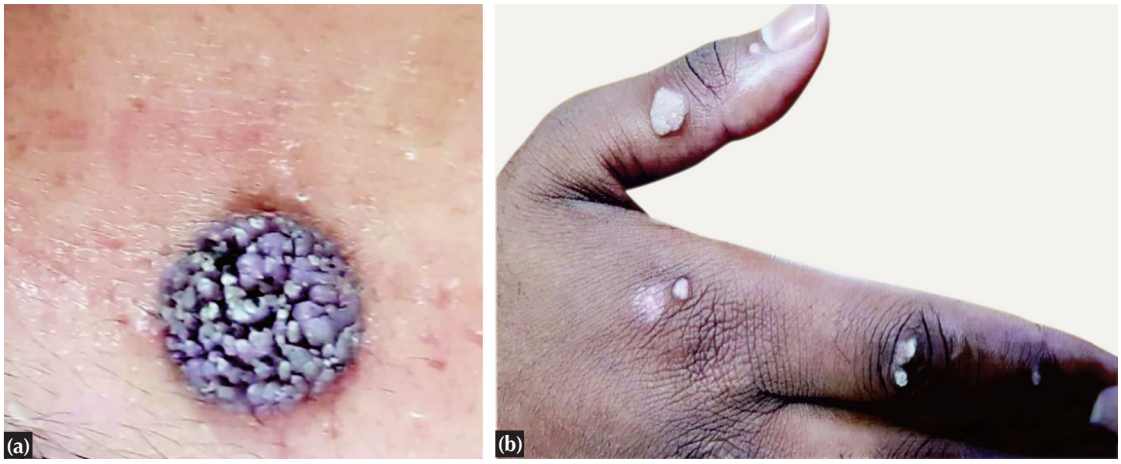
- **Causative agent:** HPV (more than 200 strains known)
- **Transmission:** Direct skin–skin contact, autoinoculation

Variants

a. Verruca vulgaris (common warts)
b. Palmoplantar warts
c. Verruca plana (plane warts)
d. Filiform warts
e. Anogenital warts
f. Epidermolysis verruciformis

Key clinical features: Hyperpigmented, hyperkeratotic lesions with verrucous surface. Pseudo Koebner phenomenon is seen.

Different type of warts are shown in (Figs 51.2a, b and c).



Figs 51.2: (a) Filiform wart (b): Verruca vulgaris on dorsum of hand (*Image courtesy:* Dermatology OPD, Government Doon Medical College, Dehradun)

Fig. 51.2: (c) Plane warts on forehead (*Image courtesy:* Dermatology OPD, Government Doon Medical College, Dehradun)

Treatment

a. Radiofrequency ablation/electric cautery
b. Cryotherapy
c. **Keratolytic agents:** Salicylic acid + Lactic acid preparations, Retinoic acid 0.05–0.1%.
d. Trichloroacetic acid (TCA) for genital warts, 60–90%

Children	Few lesions	May resolve spontaneously
Adults	Several lesions	Topical keratolytic (salicylic acid lotion, retinoic acid) chemical cautery
	Few lesions	Radiofrequency ablation/electrocautery
	Several lesions	Cryotherapy, topical keratolytic (salicylic acid lotion, retinoic acid)

2. Molluscum Contagiosum (Fig. 51.3)

- **Causative agent:** Pox virus
- **Transmission:** Direct contact
- **Clinical features:**
  - Multiple, pearly white, dome-shaped umblicated papules are present.
  - Pseudo Koebner phenomenon present
  - Any body part can be involved.
  - Characterised by presence of molluscum bodies.

Fig. 51.3: Molluscum contagiosum on nose and upper lip with impetigo on chin. (*Image courtesy:* Dermatology OPD, Government Doon Medical College, Dehradun)

Treatment

Imiquimod cream, cryotherapy, curettage and laser treatment of warts based on severity of infection.

3. Varicella Zoster (Chickenpox)

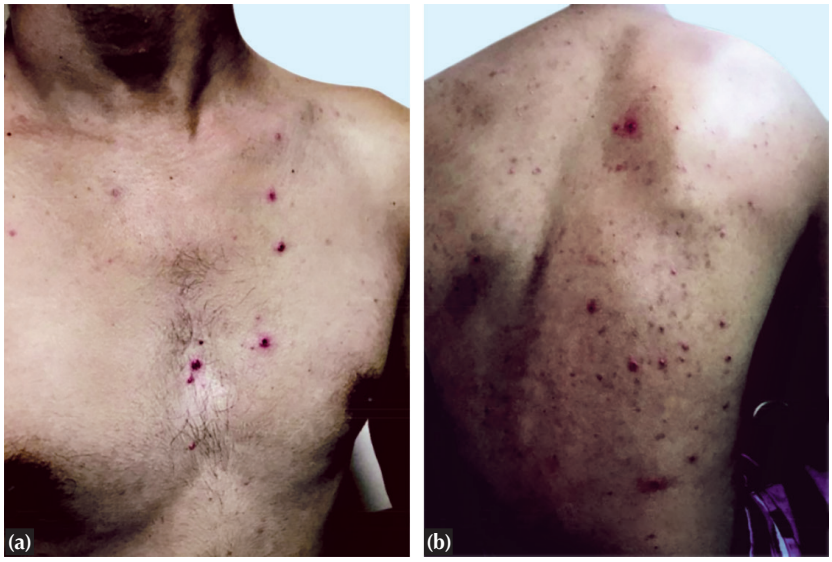
- **Causative agent:** *Varicella zoster* virus
- **Route of infection:** Droplet
- **Incubation period:** 2 weeks
- **Clinical features:** Prodrome of fever and malaise, followed by crops of papules with erythematous halo, which rapidly become vesicular (dew drops on rose petal appearance) and then pustular (Fig. 51.4).
  - Centripetal distribution
  - Polymorphous eruption (lesions of different stages present at same time)

  Diagnosis: Tzanck smear—multinucleated giant cells and acantholytic cells

  Umblicated and crusted lesions of chickenpox are seen.

Management

Pre-exposure prophylaxis: Live attenuated vaccine (developed from OKA strain, 2 doses, 3 months apart.



Figs 51.4a and b: Umbilicated and crusted lesions of chickenpox seen (*Image courtesy:* Dermatology OPD, Government Doon Medical College, Dehradun)

Post-exposure prophylaxis:

Indications:

a. Neonates whose mothers develop varicella 7 days before to 7 days after delivery
b. Healthy neonates who come in contact with active chickenpox
c. Immunocompromised adults and children coming in contact with active varicella.

Treatment with Antivirals

a. **Healthy child:** Symptomatic treatment with antipyretics and antibiotics in case of secondary infection
b. **Pregnancy:** IV acyclovir 10 mg/kg, 8 hourly for 7 days
c. **Adults with severe disease:**
   - Acyclovir, 800 mg five times a day for 7–10 days
   - Valacyclovir, 1 g, TDS for 7–10 days
   - Famciclovir, 250 mg or 500 mg for 5–7 days

4. Zoster (Shingles)

- It is a segmental eruption due to reactivation of latent VZV from dorsal root ganglion.
- **Age:** More than 50 years
- Females > males.
- Patient with immunocompromised state is more prone.
- **Clinical features:** Very painful, segmental eruption of grouped papules and vesicles on an erythematous, slightly oedematous base. Self-limiting (Fig. 51.5).
- **Sites:** Thoracic intercostal nerves, ophthalmic division of trigeminal nerve.
- **Complications:** Post-herpetic neuralgia (in elderly, when ophthalmic division of trigeminal nerve is involved and in immunocompromised). Sometimes, corneal ulcers in ophthalmic involvement. Facial palsy.

Treatment

First-line

- Acyclovir, 800 mg five times a day for 7–10 days
- Valacyclovir, 1 g TDS for 7–10 days
- Famciclovir, 250 mg or 500 mg for 5–7 days

Second-line

Acyclovir, IV

Third-line (for Post-herpetic Neuralgia)

- Amitriptyline
- Nortriptyline
- Sodium valproate
- Gabapentin
- Pregabalin

Fig. 51.5: Herpes labialis—caused by HSV 1 and HSV 2 (*Image courtesy:* Dermatology OPD, Government Doon Medical College, Dehradun)

FUNGAL INFECTIONS

1. Dermatophytic Infections

- Three genera: *Trichophyton*, *Microsporum* and *Epidermophyton*
- Prototype lesion, an itchy, annular/arcuate polycyclic lesion with clear centre and an active margin with papulovesicles and scaling.
- Scalp lesions manifest as discoid areas of non-cicatricial alopecia with easily pluckable hair.

Sites: Lesions modified by site and named variously as (Fig. 51.6):

- Tinea capitis (scalp).
- *T. faciei* (face).
- *T. corporis* (trunk).
- *T. cruris* (groin).
- *T. pedis* (feet).
- *T. mannum* (hand).
- *T. unguium* (nails).

Diagnosis

KOH mount: Fungal elements seen under microscope

Culture: Sabarouds dextrose agar used as a medium

Treatment

Localised disease:

- Topical terbinafine twice daily for 2 weeks
- Topical azole once or twice daily for 2–4 weeks

Figs 51.6: (a) *Tinea corporis*, (b) *Tinea cruris*, (c) *Tinea mannum*, (d) *Tinea pedis* (*Image courtesy:* Dermatology OPD, Government Doon Medical College, Dehradun)

Widespread disease:

- **Oral fluconazole:** 150 mg per week
- **Oral itraconazole:** 100 mg/day for 2–4 weeks
- **Oral terbinafine:** 250 mg/day for 2–3 weeks

2. Pityriasis Versicolor

- **Causative agent:** *Mallassezia globosa, M. furfur*
- **Clinical features:** Perifollicular, hypopigmented (or hyperpigmented), macules and patches surmounted with branny scales.
- **Sites:** Upper trunk, neck, upper arms.
- **Investigations:** KOH mount shows characteristic 'spaghetti and meat ball' appearance.
- **Treatment:** Topical imidazole derivatives, selenium sulfide.
- Systemic fluconazole, ketoconazole and itraconazole in extensive and recurrent lesions.

BACTERIAL INFECTIONS

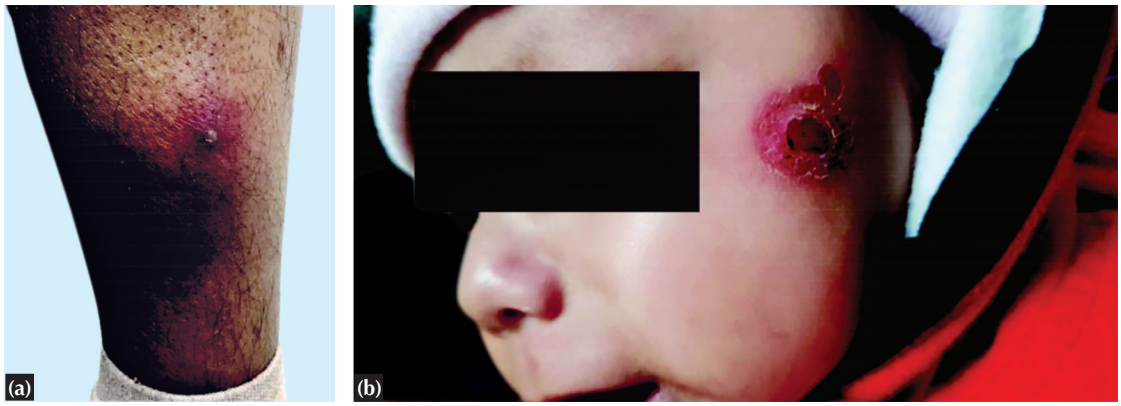
1. Pyoderma

Predominantly caused by *S. aureus* and *S. pyogenes* (Table 51.1).

(a) Impetigo contagiosa and bullous impetigo (Fig. 51.7b)

Age: Childhood

Table. 51.1: *Streptococcus* and *Staphylococcus* skin infections	
Impetigo contagiosa	***Bullous impetigo***
Causative agent: *S. aureus* and *S. pyogenes*	*S. aureus*
Prevalence: Frequent	Sporadic
Age: Children	Infants
Morphology: Thin-walled and transient	Bulla is thick walled and persistent
Erythemtous halo present	Absent
Crust: Honey coloured and thick	Thin, varnish like
Central clearing: Not seen	Present
Site: Face	Face and other parts
Treatment	***Treatment***
1. Topical fusidic acid and mupirocin	1. Topical fusidic acid and mupirocin
2. Oral erythromycin/ oral amoxiclav 25 mg/kg/day	2. Oral erythromycin/oral amoxiclav 25 mg/kg/day
Folliculitis: Papular, pustular inflammation of hair follicles (Fig. 51.7a)	
Furuncle: Painful, firm and fluctuant abscess originating from a hair follicle	



Figs 51.7a and b: (a) Folliculitis, (b) Impetigo contagiosa (*Image courtesy:* Dermatology OPD, Government Doon Medical College, Dehradun)

Scabies

- **Causative agent:** Sarcoptes scabie var hominis (mite)
- **Transmission:** Direct contact
- More common in children
- Predisposed are people with poor hygiene, immunosuppression and overcrowding.

Clinical Features

Asymptomatic for 3–4 weeks.

Excessive night time itching. Similar history in family members and close contacts. Burrows, papules and papulovesicles present in **'circle of Hebra'**.

Complicated by secondary infection, eczematisation.

Variants

1. **Classical scabies:** Burrows often located on the web spaces on the fingers and toes. Bumps anywhere on the skin. Itching is the most common symptom at night (Figs 51.8a and b).
2. **Norwegian scabies:** Seen in immunosuppressed individuals. Excessive crusting and hyperkeraotic lesions present.
3. **Infantile scabies:** Characterised by vesicles and bullae.
4. **Nodular scabies:** Few violaceous pruritic nodules are located in groin, axillae and male genitalia.

Figs 51.8a and b: Papules on trunk and hands (*Image courtesy:* Dermatology OPD, Government Doon Medical College, Dehradun)

Investigations

Direct microscopy: Visualisation of mite, eggs and scybala (mite feces)

Management

1. **Patient education:** Regarding maintaining hygiene, treatment of family members.
2. **Treatment options:**
   a. Topical 5% permethrin lotion—below neck on whole body for 8–12 hours once a week (2 applications)
   b. Topical lindane 1% lotion—6 hrs application once a week same way as permethrin
   c. Topical benzyl benzoate (25%)—rinsed off after 24 hours.

d. Topical crotamiton 10% lotion—applied twice for 24 hours each for 2 consecutive days
e. Precipitated sulphur (2–10%)—applied twice for 24 hours each for 2 consecutive days
f. Oral ivermectin—200 µg/kg stat, repeat after 7–14 days

Inflammatory Disorders

1. Psoriasis

- T-cell-mediated autoinflammatory dermatoses. Bimodal age distribution. Aggravated in winters
- **Morphology:** Well-defined erythematous plaques with silvery white scales (Fig. 51.9).
- **Sites:** Extensors > flexors, scalp, nails
- Grattage test, Auspitz sign–positive
- **Histopathology:** Epidermis—parakeratosis, spongiform pustule of Kogoj, suprapapillary thinning, elongation of rete ridges
- **Dermis:** Elongation of rete ridges, tortuous blood vessels

Types of Psoriasis

1. Guttate psoriasis
2. Eruptive psoriasis
3. Erythrodermic psoriasis
4. Pustular psoriasis
5. Rupioid psoriasis

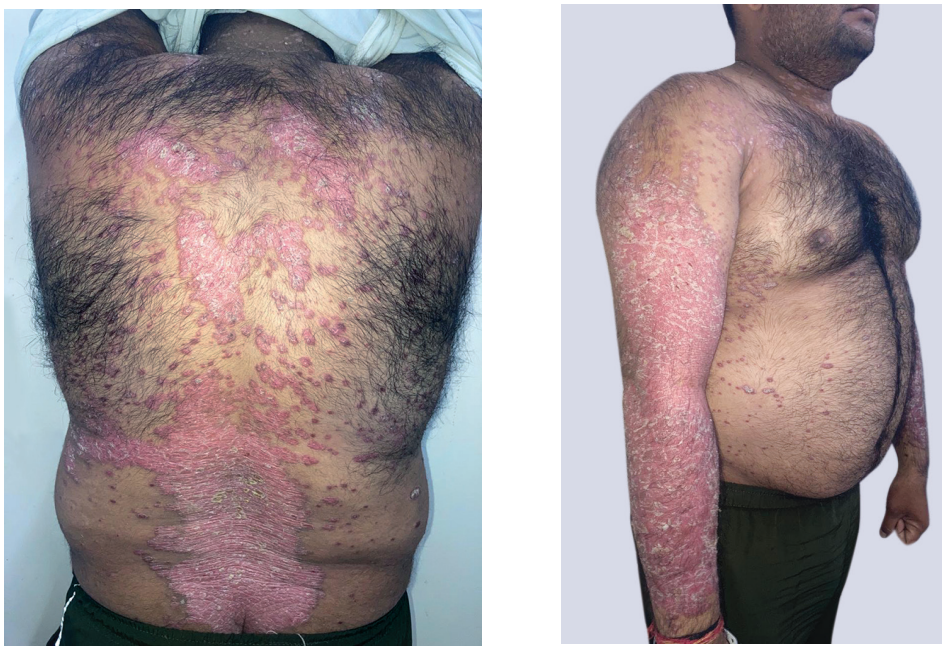


Fig. 51.9: Plaques of psoriasis (Image courtesy: Dermatology OPD, Government Doon Medical College, Dehradun)

Treatment

Mild psoriasis

- **First-line:** Coal tar, dithranol, potent topical corticosteroids, vitamin D analog
- **Second-line:** Local NB-UVB or PUVA, excimer laser

Moderate-to-severe Plaque Psoriasis

- **First-line:** NB-UVB or PUVA
- **Second-line:** Acitretin, apremilast, ciclosporin, fumaric acid esters, methotrexate
- **Third-line:** Adalimumab, etanercept, infliximb, secukinumab, ustekinumab

2. Lichen Planus (LP)

- It is an idiopathic inflammatory skin disease affecting the skin and mucous membrane (Fig. 51.10).
- **Clinical features:** Acute or insidious in onset, purple, polygonal, plane topped, pruritic, papule (5 Ps of LP), Wikham's striae present.
- **Sites:** Flexors of extremities, lower back
- Koebner phenomenon

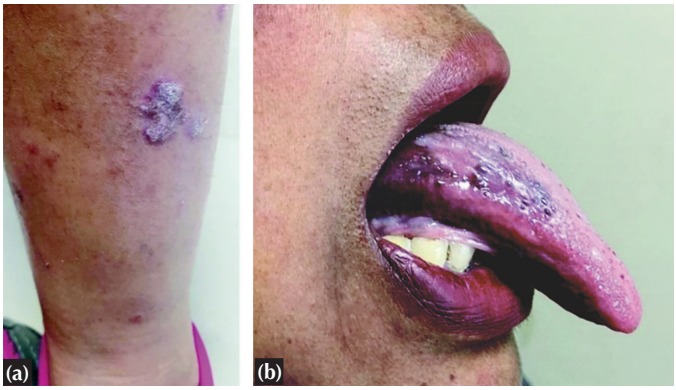
Variant of LP

1. Annular LP
2. Actinic LP
3. Follicular LP
4. Hypertrophic LP
5. Linear LP
6. Bullous LP

Oral mucosa: Involved in 50% patients with cutaneous LP.

Types of patterns seen in oral mucosa:

1. Lacy reticular pattern
2. Erosive
3. Ulcerative



Figs 51.10a and b: Cutaneous lichen planus and oral LP, respectively (*Image courtesy:* Dermatology OPD, Government Doon Medical College, Dehradun)

Nail changes

- Thinning, distal ridging of nailplate
- Pterygium
- Pup tent sign
- Trachyonychia

Treatment

Localised lesions: Topical potent corticosteroids (Clobetasol propionate, 0.05% ointment), topical tacrolimus

Widespread lichen planus (LP)—

1. Oral prednisolone 0.5–1 mg/kg/day, until improvement
2. Acitretin 30 mg/day, for 8 weeks
3. PUVA or UVB
4. Methotrexate

VITILIGO

It has autoimmune etiology with familial predisposition.

Clinical Features

Characterized by depigmented macules, which are chalky or milky white. Sometimes, pigment loss is partial and occasionally, three shades (trichrome) are seen in the same lesion—depigmented centre, surrounded by a hypopigmented rim, which in turn, has normal pigmented skin around it (Fig. 51.11).

Lesions have convex borders with few lesions having leukotrichia (white hairs).

Predisposed sites: Friction prone areas—dorsum of hands, feet, elbows and knees.

Koebner phenomenon, positive

Patterns

1. Vitiligo vulgaris
2. Segmental vitiligo
3. Generalised vitiligo

Treatment

First-line: Topical potent topical corticosteroids/topical tacrolimus/pimecrolimus
Second-line: PUVA, Excimer lamp
Third-line: Surgical technique
Melanocyte transfer—blister grafting.
Punch grafting—split thickness skin grafting.

Fig. 51.11: A patch of vitiligo before and after treatment (*Image courtesy:* Dermatology OPD, Government Doon Medical College, Dehradun)

ACNE VULGARIS

Acne vulgaris is a disorder of pilosebaceous complex which predominantly affects the peripubertal population and clinically manifests as comedones (open/closed), papules, nodules, pustules, and cysts and heals with scars (Fig. 51.12).

Clinical Features

Grade 1: Predominant comedonal acne. Comedones are either open comedones or closed come-dones

Grade 2: Predominant papules with few comedones and pustules

Figs 51.12a and b:

Grade 3: Predominant lesions are pustules with few papules and comedones

Grade 4: Nodulocystic lesions present

Typical distribution: Face, shoulders, upper part of trunk and chest.

Variants of Acne

1. Acne conglobata
2. Acne fulminans
3. Cosmetic acne
4. Steroid induce acne
5. Occupational acne
6. Acne excoree
7. Infantile acne
8. Late onset acne

Treatment of Acne (Table 51.2)

Table. 51.2: Treatment of acne according to severity of infection

Drugs	*Mild*		*Moderate*		*Severe*
	Comedone	Papulopustular	Papulopustular	Nodular	Nodular/conglobata
Drug of choice	Topical R	Topical R + Topical Ab/BP	Oral Ab + Topical R + BP	Oral Ab + Topical R + BP	Oral R
Alternatives	Alternative topical R/Ab/AzA	Alternative topical R/Ab/AzA	Alternative oral Ab + topical Ab + BP	Oral R	Oral Ab + topical R + BP
Maintainance	Topical R	Topical R	Topical R	Topical R	Topical R
Females	–	–	–	Oral AA + topical R oral R under supervision	Oral AA + topical R oral R under supervision

R—retinoid, Ab—antibiotic, BP—benzoyl peroxide, AzA—Azelaic acid, AA—antiandrogen

MELASMA

It is a skin disorder that causes patches and spots on face darker than natural skin. These cells become hyperactive and produce too much pigmentation in certain areas of skin. It can occure in pregnancy in women taking oval contraceptives and hormones.

Treatment

- Sun protection, use sunscreens
- Hydroquinone topical
- Tretinoin and a mild corticosteroid (a retinoid)
- Triple combination therapy-retnoil and corticosteroid to reduce inflammation, hydroquinone to even out skin tone.
- Azelaic acid kojic acid or vitamin C

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Chapter
52

Treatment in Dental Practice

A. ANALGESICS USE IN DENTAL TREATMENT

INTRODUCTION

Pain is a common complaint among patients presenting for emergency care at a dental clinic. Pain may arise from different structural or anatomical origins of odontogenic or non-odontogenic sources. A significant amount of dental pain originates from acute and chronic pulpal infection. Pain response comes from the inflammatory reactions originated due to tissue distortion, disturbance of the adjacent soft tissues and periodontal structures. Diagnosing and eliminating the cause is the main task, as, most cases are related to the treatment of the pulpal pathology. Pain management is followed by the 3 "D" principle of—*diagnosis, dental treatment, and drugs*.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs for managing surgical pain and inflammation. Consistently, NSAIDs are routinely prescribed for mild-to-moderate dental pain and are supplemented/replaced by opioid analgesics in severe pain. The steroids as adjunctive measures to reduce post-operative inflammation, swelling, and pain has been used.

Classification of Analgesics Used in Dental Practice

Classification of analgesics
Opioid analgesics
Hydrocodone, oxycodone, codeine, tramadol
Non-opioid analgesics
NSAIDs
tNSAIDs
Diflunisal, ibuprofen, naproxen, ketoprofen, loxoprofen, flurbiprofen, indomethacin, sulindac, etodolac, diclofenac, ketorolac, piroxicam, meloxicam, mefenamic acid, nabumetone
COX-2 inhibitors (COX-2-selective NSAIDs)
Celecoxib, etoricoxib, polmacoxib
Acetaminophen
Drugs used for neuropathic pain
Pregabalin, gabapentin, duloxetine

NSAIDs: Non-steroidal anti-inflammatory drugs, tNSAIDs: traditional non-steroidal anti-inflammatory drugs, **COX-2:** cyclooxygenase-2.
In Korea, tramadol is approved as a non-narcotic analgesic.

OPIOID ANALGESICS (Table 52.1)

Opioid analgesics, such as hydrocodone, codeine, oxycodone, and tramadol, for the management of dental pain are often prescribed. However, opioids may cause various adverse effects, such as nausea and vomiting, constipation, urinary retention, respiratory depression, sedation, sleep disturbance, dependence, and addiction. In contrast, non-opioid analgesics generally have less serious adverse effects than opioid analgesics at therapeutic doses. Clinical studies have repeatedly shown that non-opioid analgesics, such as ibuprofen, are more effective than opioids in suppressing postoperative dental pain. In cases where non-opioid analgesics fail to relieve pain, an opioid may be administered in conjunction with non-opioid analgesics to provide synergistic analgesia.

Table 52.1: Opioid analgesics

Product	*Duration, h*	*T1/2 beta (hour)*	*Equianalgesic doses, IM/PO*
Hydromorphone	4–5	2–3	1.5/7.5 mg
Morphine	3–7	15–5	10/30 mg
Methadone	4–6	15–30	10/20 mg
Meperidine	2–4	3–4	75–100/300 mg
Codeine	4–6	3	120/180–200 mg
Hydrocodone	4–8	3.3–4.5	ND/30 mg
Oxycodone	4–6	ND	NA/20 mg*
Propoxyphene	4–6	6–12	ND/200 mg

*NA indicates not available for IM use in the United States ND, no data available.

ACETAMINOPHEN

Acetaminophen (also known as paracetamol) is one of the most widely used analgesic, antipyretic drugs and has minimal anti-inflammatory activity. Due to no inhibitory effect on the peripheral COX activity, acetaminophen is less likely to induce gastrointestinal and cardio vascular adverse effects and does not prolong bleeding time. Acetaminophen can be safely used in pregnant women. However, acetaminophen may cause serious liver damage, if used in excessive quantities, as its toxic metabolites are generated. Thus, this drug should not be taken in excess of 4 g per day (the United States Food and Drug Administration), and those with serious liver disease or who regularly and continuously consume large volumes of alcohol should exercise extra caution. Acetaminophen is used for mild pain and can be combined with NSAIDs and/or opioid analgesics to increase effectiveness.

Adverse Effects

Those taking enzyme-inducing drugs (e.g. anti-epileptics and rifampicin) increase PCM toxicity. Paracetamol may cause prolongation of prothrombin time in patients taking anticoagulants and it may cause urticarial or erythematous skin rashes, fever or blood dyscrasias. An overdose of paracetamol is when a single dose of more than 100 mg/ kg of body weight. Overdose will produce hepatotoxicity, hypoglycemia and acute renal tubular necrosis.[10, 11]

NSAIDs

The NSAIDs available include aspirin, diflunisal, ibuprofen, naproxen, ketoprofen, flurbiprofen, indomethacin, sulindac, etodolac, diclofenac, ketorolac, piroxicam, mefenamic acid, and nabumetone (Table 52.2). NSAIDs reduces the production of prostaglandins, an effect that is attributed to the inhibition of COX. NSAIDs inhibit both COX-1 and COX-2 to different degrees. These drugs have common therapeutic actions, including anti-inflammatory, analgesic, and antipyretic actions due to the inhibition of COX-2, the expression of which is induced by inflammation. In contrast, the inhibition of COX-1 is generally responsible for NSAID- induced gastropathy, nephropathy, and prolonged bleeding time. The duration of prescription ranges from a self-medication preference or 'stat-on-symptoms' approach to the medication being prescribed for 2 to 9 days post-surgically.

To choose the most appropriate analgesic for pain relief, dentists should consider both the potential benefits and the risks. From the perspective of benefit-risk analysis, the primary drugs of choice of dental pain are acetaminophen and ibuprofen.

Ibuprofen is one of the most frequently prescribed analgesics for dental pain as it is very effective for relieving mild or moderate pain, Within its dose range, the potential of ibuprofen to cause adverse gastrointestinal, liver, or cardio vascular effects is relatively low compared with other NSAIDs.

Naproxen has a longer duration and better anti-inflammatory effect than ibuprofen. However, despite its advantages over ibuprofen, naproxen has a higher risk of adverse effects such as gastrointestinal toxicity. Thus, naproxen must be reserved for pain that is not relieved by ibuprofen.

Table 52.2: Non-opioid analgesics

Product	*Dosage*
Ibuprofen (Motrin)	400–800 mg tid/qid
Flurbiprofen (Ansaid)	50–100 mg tid
Ketoprofen (Orudis)	25–75 mg tid/qid
Naproxen sodium (Anaprox)	550 mg bid
Diflunisal (Dolobid)	1000 mg STAT, then 500 mg q^{8}-12h
Diclofenac potassium (Cataflam)	50–100 mg STAT, then 50 mg tid
Celecoxib (Celebrex)	200 mg qd/bid
Acetaminophen (Tylenol)	500–1000 mg tid/qid

Acetaminophen and those nonsteroidal anti-inflammatory drugs (NSAIDs) most often used as non-opioids for management of postoperative pain and inflammation

Selective COX-2 Inhibitors

Selective COX-2 inhibitors are used to avoid the adverse gastrointestinal and bleeding-associated effects caused by COX-1 inhibition. However, these drugs might increase the risk of thrombosis and have been reported to have serious cardiovascular side effects. Therefore, COX-2 inhibitors should be used carefully, and dentists are advised to avoid these drugs in patients at high risk of cardiovascular disease.

ADVERSE EFFECTS/CONTRAINDICATIONS OF NSAIDs USE

Drug–drug Interactions (Table 52.3)

NSAIDs are associated with a range of drug interactions. For example, NSAIDs such as ibuprofen and naproxen have been reported to interact with aspirin. NSAIDs, are contraindicated in patients who have experienced bronchospasms, angioedema, and allergic reactions to aspirin. Many patients with cardiovascular diseases take low dose of aspirin regularly to decrease the risk of ischemic heart disease and stroke. Ibuprofen or naproxen is not prescribed to patients taking aspirin, as it interferes with the antiplatelet effect of aspirin by antagonizing the acetylation of COX-1 and will thus reduce aspirin's cardio protective effects. If these NSAIDs are deemed necessary, patients should be informed about this drug interaction and should be advised to take aspirin at least 30 minutes prior to taking such NSAIDs.

Consumption of antacids might decrease the absorption of NSAIDs. The concurrent use of corticosteroids may increase the risk for NSAID-induced gastropathy. Due to decreased renal clearance of the drug, the actions of lithium when taken with NSAIDs may be increased. Also, due to the high protein binding of NSAIDs the effects of oral hypoglycemic agents and

Table 52.3: Drug interactions associated with NSAIDs

Drugs interacting with NSAIDs	*Effects*
Oral antidiabetic drugs	Hypoglycemia may occur
Low-dose aspirin	The cardiovascular protective effects of aspirin may be compromised
ACE inhibitors—blockers, and diuretics	Blood pressure may increase
Antiplatelets or anticoagulants	Bleeding tendency and increase
Other NSAIDs	NSAID-related adverse effects may increase
Corticosteroids	Averse gastrointestinal effects may increase
Methotrexate, lthlum, phenytoin, and calcium channel blockers	Toxicity may increase due to elevated blood level of these drugs
Nephrotoxic agents, such as adefovir, aminoglycosides, clsplatin, and foscarnet	Risk of renal damage may incease

NSAIDs: Non-steroidal anti-inflammatory drugs, ACE: Anglotensin-converting enzyme

phenytoin may be increased. NSAIDs may cause fluid retention and consequently increase the potential to aggravate congestive heart failure. Additionally, these agents may elevate blood pressure or reduce the effects of antihypertensive drugs. Renal function must be monitored in patients who take both a NSAID along with diuretic or angiotensin-converting enzyme inhibitor.

Celecoxib is contraindicated in patients with severe hepatic damage. They are not recommended for use in patients younger than 18 years of age, and dosage adjustments are not much needed in the elderly.

Gastrointestinal Effects

Although NSAIDs are safe if used for a short period of time, they may cause heartburn, nausea, vomiting, diarrhea and sometimes gastric ulcer and gastric perforation. In patients at high risk of gastrointestinal disease, NSAIDs is prescribed in combination with proton pump inhibitors. Alternatively, acetaminophen or COX-2 inhibitors can be prescribed.

Omeprazole is administration at a dose of 20 mg/day affords a 90–95% reduction in 24-hour gastric acid output.

Ranitidine is a specific histamine H-2 receptor antagonist which is administered at a dose of 150 mg every 12 hours, and usually via the oral route.

Cardiac Risk

These patients may deteriorate or have an acute cardiac event with moderate-to-high-dose NSAID use and the risk depends upon the strength of the drug, the dose given and the duration of treatment. Ibuprofen must be restricted to a maximum of 1,200 mg daily and diclofenac should be avoided.

Pediatric

Analgesia for children is an important part of pediatric dentistry. Dentist can prescribe paracetamol and ibuprofen for use in children and the standard doses for each age group are given in Table 52.5. Aspirin and diclofenac should not be used. Children should not be given prolonged courses of analgesia using this regime beyond two weeks.

ANALGESIC USE IN RENAL AND HEPATIC INSUFFICIENCY

For NSAIDs, dose reduction or avoidance is indicated in advanced stages of renal failure. But special caution should also be exercised in patients with end-stage renal disease without dialysis where by the use of opioids such as codeine, dihydrocodeine, dextropropoxyphene and hydrocodone is not recommended (tramadol may be used with caution).

Antiplatelet Action

The non-selective inhibition of cyclo-oxygenase induced by the conventional NSAIDs induces reduction in thromboxane A2 synthesis, which leads to the inhibition of platelet aggregation–an important step in hemostasis. This is relevant in dental practice as surgical intervention might be required in some patient to treat dental pain.

Effects on Blood Pressure

Another adverse effect of NSAIDs is arterial hypertension (AHT). Since the rises in blood pressure associated to NSAIDs have been found to accumulate in patients with treated arterial hypertension, with only small and non-significant increments in normotensive individuals, it has been suggested that NSAIDs could antagonize the effects of anti-hypertensive drugs. The results published by Johnson et al., support this idea.

Analgesics Used in Pediatric Age Group (Table 52.4)

Table 52.4: Analgesic use in kids

Dental pain	*Treatment*	*Dose for each age group*
For dental pain in children, an appropriate five-day regimen is either:	Paracetamol (500 mg tablets, or 120 mg/5 ml or 250 mg/5 ml oral suspension), dose depending on age, up to four times daily (max. = four doses in 24 horus)	6–12 moths = 120 mg 2–3 years = 180 mg 4–5 years = 240 mg 6–7 years = 240–250 mg 8–9 years = 360–375 mg 10–11 years = 480–500 mg 12–15 years = 480–750 mg 16–17 years = 500 mg–1 g
	Ibuprofen (200 mg tablets, or 100 mg/5 ml oral suspension), dose depending on age, preferably fter food up to three times daily unless indicated otherwise	6–11 moths = 50 mg (four times daily) 2–3 years = 100 mg 4–6 years = 150 mg 7–9 years = 200 mg 10–11 years = 300 mg 12–17 years = 300–400 mg

Use of NSAIDs in Pregnancy

According to Ostenten, et.al., the classical, non-selective COX inhibiting NSAIDs may be associated with infertility and miscarriage. Paracetamol is adequate during pregnancy, though it is advisable to prescribe the drug in consultation with an obstetrician.

COVID-19

Currently there is no guidance in the literature suggesting that changes should be made to analgesia regimes for dental patients with COVID symptoms nor to support avoiding ibuprofen in this group, despite the large numbers infected since the virus was first reported. At present, the same analgesic plan should be used for both COVID-positive and negative primary care patients.

Conclusion

Non-prescription analgesic use is common in patients and a significant number of these patients over use these products. Non-steroidal anti-inflammatory drugs are the most frequently misused products, but patients also overuse acetaminophen. This overuse may place patients at increased risk for adverse events from these products.

When dentists prescribe analgesics, they should consider the severity of the patient's pain, the pharmacological properties of the drug, the patient's history of systemic disease, and potential interactions with drugs the patient is taking. Non-opioid analgesics have been shown to exhibit a safe profile when used for acute dental pain, and the overall risk of these drugs as their use in dentistry is low. Acetaminophen, ibuprofen and naproxen appear to be the safest non-opioid drugs considering the evidence regarding gastrointestinal and cardiovascular safety.

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B. ANTI-HEMORRHAGIC AGENTS IN DENTAL PRACTICS

Oral surgical procedures in patients with bleeding disorders might require hospitalization in rare cases. Post-operative bleeding management of patients on oral anticoagulant therapy (warfarin or heparin) or with bleeding disorders (von Willebrand disease, hemophilia, factor V, VII, X and XIII deficiency) usually requires local treatments to maintain the blood levels of anticoagulation and achieve hemorrhage control at the same time. These procedures include synthetic vasopressin packaging and infusions, absorbable gelatin sponges and fibrin sealants or clotting factor concentrates.

PASSIVE HEMOSTATIC AGENTS' COLLAGEN-BASED PRODUCTS

Hemostatic collagen products are derived from either bovine tendon or bovine dermal collagen and are non-toxic and non-pyrogenic and may be further divided into microfibrillar and absorbable collagen products. Microfibillar collagen is derived from purified bovine dermal collagen; it is a fibrous, water-insoluble partial hydrochloric salt. It attracts platelets and stimulates aggregation of platelets into thrombi in the interstices of the fibrous mass resulting in the formation of a physiologic platelet plug, degranulation, and release of clotting factors, thus initiating the clotting cascade.

Absorbable Collagen Hemostat Sponge

It is collagen derived from purified and lyophilized (i.e. freeze-dried) bovine flexor tendon and is available as soft, white, pliable, non-friable, coherent, sponge-like structures. The products are extremely absorbent and able to hold a lot of fluid. It is indication for wound protection and for control of oozing or bleeding from clean oral wounds. These products are to be held in place for 2–5 minutes to attain hemostasis and then may be removed, replaced, or left *in situ*.

Cellulose-based Products Oxidized Regenerated Cellulose (Surgicel)

It is derived from plant-based alpha-cellulose and is available in an absorbable white, knitted, fabric (single or multiple sheets) that is of either high- or low-density. It is prepared as a sterile fabric mesh work and is expensive. It provides an absorbable physical matrix for clotting initiation, expands on contact with blood 7–10 times its own weight. The rate at which the body absorbs, it depends on the amount used, the extent of blood saturation, and the tissue bed. Absorption of Surgicel will occur in approximately 4–8 weeks. It should not be used (1) in closed spaces because of swelling, (2) on bony defects (fractures) as it may interfere with bone regeneration, and (3) for control of hemorrhage from large arteries. Adverse reactions include: (1) encapsulation of fluid and foreign body reaction, if the product is left in the wound, (2) stenosis of vascular structures if cellulose is used to wrap a vessel tightly, (3) burning sensation when placed in unanesthetized nasal passages. Excessive amounts of the material should be removed if possible, to prevent delayed healing, (4) surgical granulomas, and (5) neurological complications.

Gelatin-based Product Gelfoam

One of the more commonly employed agents for the control of minor bleeding. Gelfoam is a porous, pliable, absorbable gelatin sponge that is prepared from purified pork skin gelatin. It

is manufactured as films, gelatin sponges (Gelfoam), or powder that is mixed to form a paste. This product has properties that allow it to absorb about 40 times its weight in blood, and it can expand to 200% of its initial volume. It provides a clotting framework and effectively arrests small vessel bleeds, but large arterial bleeds may dislodge gel foam. Gel foam has very little tissue reaction and liquefies in the oral cavity within a week, fully absorbing within 4–6 weeks. It is very useful in managing post-operative bleeding after dental extractions and addition of thrombin improves its efficacy. Gelatine-based devices have been reported to induce a better-quality clot than collagen-based hemostats.

ACTIVE HEMOSTATIC AGENTS

Thrombin

Topical thrombin products are derived from either bovine or human plasma, or they are manufactured using recombinant DNA techniques (i.e. recombinant thrombin). Thrombin may be used topically as a dry powder, as a solution for use with gelatin sponges, mixed with a gelatin matrix, or as a spray. It has a rapid onset of action (e.g. within 10 minutes). It converts fibrinogen to fibrin. It is commonly used with gel foam to treat moderate to severe bleeding. Thrombin should never be injected in to the blood stream or allowed to enter the blood stream through large, open blood vessels because it can cause extensive intravascular clotting which can be fatal.

FloSeal (Flowable Hemostatic Agent)

FloSeal matrix hemostatic seal is antiproprietary combination of two independent agents and consists of bovine-derived gelating granules coated in human-derived thrombin that works in combination to form a stable clot at the bleeding site. When applied to a bleeding site, the gelatin granules swell byabout 10–20% as it contacts blood, causing a seal at the bleeding site. The thrombin portion of the product activates the common pathway of the coagulation cascade and converts fibrinogen to a fibrin polymer, forming a clot around the stable matrix. It is resorbed by the body within 6–8 weeks, consistent with the time frame of normal wound healing.

HEMOSTATIC SOLUTIONS

Styptics

Styptics, e.g. aluminum solutions when applied locally cause hemostasis by contracting tissue to seal injured blood vessels.

Tannic Acid

Tannic acid is a commercial compound that is similar to the plant polyphenol tannin, which stops bleeding from mucous membrane via vasoconstriction.

Lysine analogs—tanexamic acid, epsilon-aminocaproic acid.

Tranexamic Acid

Tranexamic acid 4.8% oral rinse is an antifibrinolytic agent that stabilizes clots and facilitates clot formation by competitively inhibiting plasminogen, the enzyme responsible for activating plasmin. The main role of plasmin in the body is clot degradation or fibrinolysis; hence, tranexamic acid non-competitively inhibit plasmin and stabilizes clot formation. Oral

tranexamic acid has been shown to be beneficial in the management of patients with both inherited and acquired bleeding diatheses under going minor oral surgeries. It can also be useful as a prophylactic mouthwash in patients who are on anti-coagulant medications which require oral surgery. It can be used preoperatively, intra operatively, or post operatively to manage bleeding.

Epsilon Aminocaproic Acid

It is an antifibrinolytic agent, less potent than tranexamic acid but can be used as an alternate to it.

Hemocoagulase (Botroclot)

Hemocoagulase is based on the coagulative and antihemorrhagic properties of those fractions isolated from the venom of 'Bothrops jararaca' or 'Bothrops atrox'. Hemocoagulase reduces the bleeding time and promotes wound healing by promoting the growth of capillaries in wound space. Hemocoagulase has two different enzymatic activities, which promote blood coagulation. One of these accelerates the conversion of prothrombin to thrombin (thromboplastin-like enzyme) while the other one causes a direct transformation of fibrinogen to fibrin monomer, which can be converted by thrombin into fibrin clot (thrombin-like enzyme).

Contraindications: Venous and arterial thrombosis, disease with tendency to intravascular coagulation. In a study conducted by Majumder, et al. it was found that hemocoagulase topical solution when used after minor oral surgery not only provides faster hemostasis but also enhance healing.

BONE HEMOSTATS

Bone Wax

Bone wax is a sterile mixture of water-insoluble beeswax, paraffin, and isopropyl palmitate (a softening agent) that is packaged in individual foil envelopes and is useful when bleeding is from a visualized local vascular channel within bone, commonly referred to as a "bone bleeder", at the surgical site.

Ostene

It is a bone wax-like preparation of water-soluble alkylene oxide co polymers. It is a synthetic bone hemostatic material first used in cranial and spinal surgeries. It is inert and removed from the body unchanged within 48 hours. It avoids the negative effects of bone wax, as it does not cause infection, inflammatory reactions, or interference in the osseous union.

SUMMARY

Hemostasis is an integral and am important aspect of surgical practice. The first step in bleeding control is direct pressure, and hemostatic agents should always be considered secondary. A thorough knowledge about these agents is necessary to make the right choice of them when required. Factors affecting the selection of an appropriate topical hemostat include the type of procedure, cost, severity of bleeding, site of bleeding, systemic condition of the patient and the personal experience and preference of the surgeon.

C. ANTIBIOTICS AND THEIR USE IN DENTAL PRACTICE

INTRODUCTION

The human oral cavity contains a broad range of microorganisms, more than 500 different species, and Liebana, et al. reported that all known microorganisms associated with humans are at some time found in the oral cavity as either transient (the majority) or resident (only a few) species. In this sense, the microbiology is varied, and multiple microorganisms with different characteristics can be involved. When the pulp tissue gets necrosed, the bacteria advance through the pulp canal and it progresses towards periapical inflammation. The recommended treatment for these forms of dental pain is removal of the associated bacteria by removing necrosed nerve, by extraction of the tooth or root canal treatment. The presence of peri-apical infection warrants the rationale for the systemic administration of the antibiotics. Antibiotics are routinely prescribed in dental practice for both prophylactic and therapeutic use. Dentists prescribe medications for the management of a number of oral conditions, chiefly for orofacial infections. Antibiotic prescription is decided on a presumptive basis, as what microorganism is responsible for the infection as cultures are not regularly grown from the patient's pus or exudate.

When Antibiotics Should be Indicated

Antibiotics are not an alternative to dental intervention; rather they are adjunctive to clinical intervention. The major use of antibiotic prophylaxis in dental procedures is for procedures that cause bleeding in the oral-cavity, and administration of antibiotics for such cases has become common practice among dentists. Antibiotics are frequently indicated in dental practice for treating immuno-compromised patients, patients with evident signs of systemic infection and if the signs and symptoms of infection progress rapidly.

Antibiotics are typically prescribed in dental practice:

1. For the treatment of acute and chronic infections of odontogenic and non-odontogenic origins.
2. As prophylactic treatment prevents focal infection in patients at risk (as a result of systemic conditions such as endocarditis, artificial heart valves and congenital heart disease).
3. To prevent local infection and systemic spread among patients undergoing surgical oral or dental treatment.
4. In surgical excision of benign tumors.
5. In immuno-compromised patients.

Antibiotics for Odontogenic Infections

A considerable percentage of pain of dental origin originates from acute and chronic infections of pulpal origin, in ulcerative necrotizing gingivitis, in periapical abscess, in aggressive periodontitis and in severe infection of the fascial layers and deep tissue of head and neck, which necessitates operative intervention, rather than antibiotics. Non-indicated clinical cases for oral antibiotic use, include acute periapical infection, dry socket and pulpitis (Table 52.5). Represents use and no use of antibiotics in various dental conditions.

Table 52.5: Antibiotics use in dental condition

Dental conditon	*Antibiotics (yes/no)*	*Recommended treatment depending on prognosis*
Periapical pathologies		
Asymptomatic chronic periapical pathology (Fig. 52.1)	No	Extraction teeth or endodontic therapy
Acute periapical abscess with no signs of fever or chills	No	Incision and drainage followed by endodontics or extraction
Periapical abscess with fever (Fig. 52.3)	Yes	Incision and drainage followed by endodontics or extraction
Periapical pathology progressed into cellulitis	Yes	Incision and drainage followed by endodontics or extraction along with antibiotics
Discharge from endodontically treated teeth	No	Repear endodontic therepy
Oral surgical conditions		
Asymptomatic third molar extractions (Figs 52.2 and 52.5)	No	Extraction and local debridement of the healing soket
Third molar extraction with concurrent periocoronitis	Yes	Extraction and local debridement of the heading socket with antibiotics
Orthognatic surgical procedures with high risk of infection and intra oral approach (Fig. 52.7)	Yes	Both preoperative and postoperative antibiotic cover required
Mandibular fractures without oral communication	No	Stabilization of fracture site with symptomatic therapy
Mandibular fractures with oral communication (Fig. 52.8)	Yes	Both preoperative and postoperative antibiotic cover required. In case of high risk of infection prophylactic antibiotic 3–5 days postoperative is required in addition
Major head and neck surgery	Yes (pre-operative)	Preoperative antibiotic therapy required. In case of high risk of infection prophylactic antibiotic 3–5 days postoperative is required in addition
Dental implants (Fig. 52.6)	Yes (pre-operative)	Preoperative antibiotic is required in case of high-risk patients
Mucosal and periodontal conditions		
Traumatic ulcers	No	Removal of trauma and symptomatic therapy with rinses and analgesic gels
Denture-induced hyperplasia (symptomatic or asymptomatic)	No	surgical removal of tissue. Denture care instructions and symptomatic therapy
ANUG (Fig. 52.4)	Yes	Scaling, maintenance of oral hygiene, mouth rinses, and antibiotics
Acute and chronic periodontitis	No	Minor surgical procedues and maintenance of oral hygiene
Recurrent/refractory and agressive periodontitis with or without high-risk	Yes	Conventional periodontal therapy and maintenance along with antibiotic cover
Avulsion and reimplanatation	Yes	Splinting along with antibiotics
Oro antral fistula	No	Surgical closure
Dentigerous and other asymptomatic cyst	No	Complete enucleation

ANUG: Acute necrotizing ulcerative gingivitis

Antibiotics for Non-odontogenic Infections

Non-odontogenic infections include specific infections of the oral cavity (tuberculosis, syphilis, leprosy), and non-specific infections of the mucosal membranes, muscles and fascias, salivary glands and bone. Bone infections are included here on the grounds that many of them may be of dental origin.

Fig. 52.1: Buccal swelling and inflammation due to caries and retained roots left infraorbital space swelling due to maxillary tooth caries

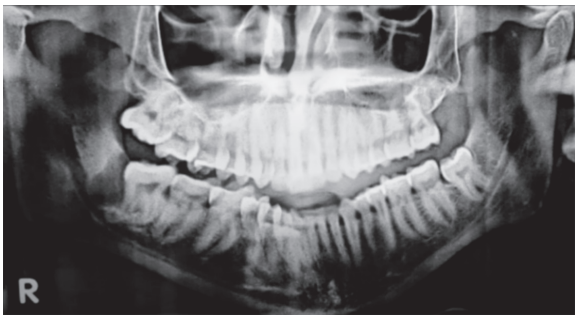

Fig. 52.2: Left—OPG-associated with pathology right 3rd molar

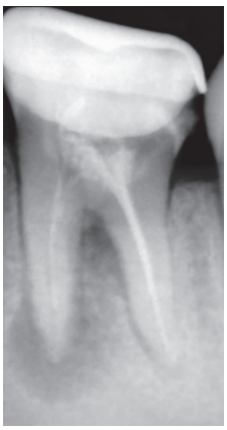

Fig. 52.3: Tooth associated with periapical infection in bone

Fig. 52.4: Necrotizing fasciitis associated with odontogenic infection

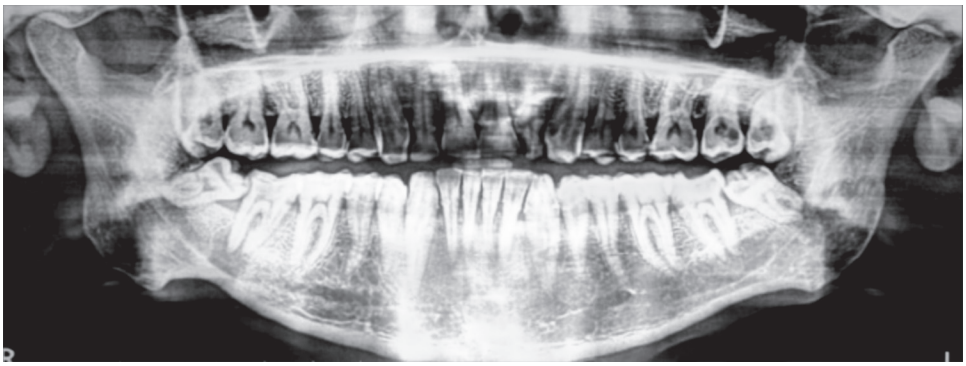

Fig. 52.5: OPG showing right 2nd and 3rd molar infection—periapical involvement

Fig. 52.6: Intraoral picture showing grossly decayed teeth

Fig. 52.7: Same patient having extraoral sinus opening due to odontogenic infection

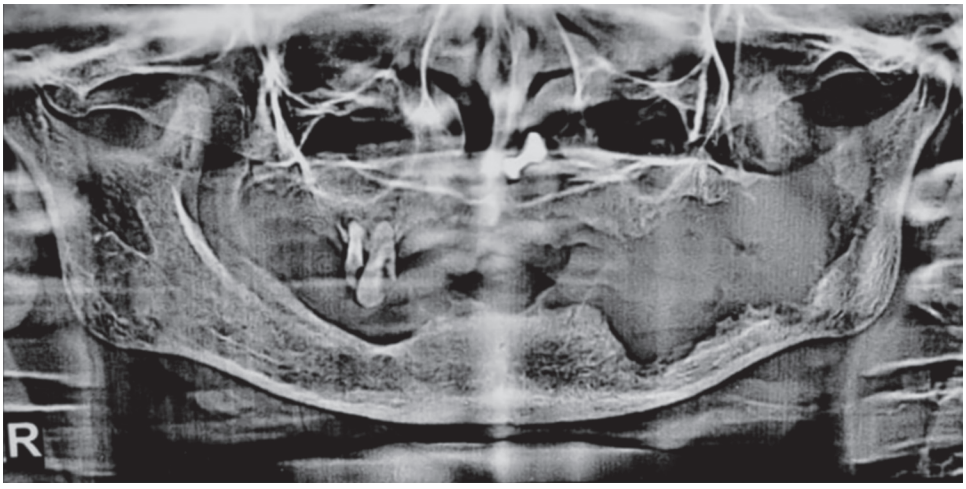

Fig. 52.8: Radiograph of a patient showing osteomyelitis of left mandible (*Images courtesy:* Dental OPD, Government Doon Medical College, Dehradun)

Prophylaxis of Focal Infection

The paradigm of this model of treatment is the prevention of bacterial endocarditis, indicated in risk patients in the context of any invasive procedure with in the oral cavity and following the guidelines of the American Heart Association (AHA) (Table 52.6). Nevertheless, there are doubts in relation to this practice. Firstly, transient bacteremia occurs not only after dental treatments such as extractions (35–80%) or periodontal surgery (30–88%). It also occurs in the context of tooth brushing (40%) or while chewing gum (20%), and is proportional to the trauma caused and to the number of germs colonizing the affected zone. Secondly, not only bacteria cause endocarditis, and of those that do cause the disease, many are resistant to the antibiotics administered as prophylaxis (fundamentally amoxicillin). Lastly, it is known

Table 52.6: Antibiotics prophylaxis against endocarditis in procedures (AHA)			
Antibiotic	***Indication***	***Dose***	***Timing***
Amoxicillin	Standard	2 g PO, *50 mg/kg/po	1 hour before
Ampicillin	If oral route cannot be used	2 g IM, or IV **50 mg im or IV	½ hour before
Clindamycin	Allergy to penicillin	600 mg PO, *20 mg/kg	1 hour before
	Allergy to penicillin and oral route cannot be used	600 mg PO, ***20 mg/kg IV	
Cephalexin or cefadroxil	Allergy to penicillin	2 g PO, *50 mg/kg/PO	½ hour before
Azithromycin or clarithromycin	Allergy to penicillin	500 mg PO, *15 mg/kg PO	1 hour before
Cefazolin	Allergy to penicillin and oral route cannot be use		½ hour before

*PO: Oral route, **IV: Intravenous route; ***IM: Intramuscular route

that most cases of bacterial endocarditis are not related with invasive procedures, and that dental care is only responsible for a minimum percentage of cases of the disease. Despite the mentioned conveniences, antibiotic prophylaxis is still recommended in patients at risk.

Prophylaxis of Local Infection and Systemic Spread

Prophylaxis of local infection is taken to comprise the administration of antibiotics on a pre-intra- or postoperative basis, to prevent bacterial proliferation and dissemination within and from the surgical wound. The use of antibiotic prophylaxis in dental surgery and procedures, in a healthy patient was only recommended in the case of the removal of impacted teeth, periapical surgery, orthognathic surgery, implant surgery, bone grafting and surgery for benign tumors. In subjects with risk factors for local or systemic infection, including oncological patients, immune suppressed individuals, and patients with metabolic disorders such as diabetes, and splenectomized patients, prophylactic antibiotic coverage should be provided before attempting any invasive procedure. The use of antibiotics in endodontics should be reserved for patients with signs of local infection, malaise or fever. Prophylactic or preventive use should be reserved for endocarditis and the systemic disorders commented above avoiding indiscriminate antibiotic use.

Appropriate Selection of Antibiotic: Dosage and Duration

Oral antibiotics that are effective against odontogenic infections include penicillin, clindamycin, erythromycin, cefadroxil, metronidazole and the tetracyclines. The type of antibiotic chosen and its dosage depend on the severity of infection and the pre dominant type of causative bacteria. The most commonly used antibiotics in dental practice is amoxicillin, followed by penicillin V, metronidazole and the combination of amoxicillin and clavulanic acid. Patients who are allergic to penicillin should benefit from clindamycin 300 mg; which is active against some oral anaerobic and facultative bacteria and has the advantage of good bone penetration. The ideal duration of antibiotic treatment is the shortest cycle capable of preventing both clinical and microbiological relapse. Most acute infections are resolved within 3–7 days. With oral antibiotics use, a high dose should be considered to facilitate achieve therapeutic levels more rapidly.

The first generation cephalosporins like cephadroxil, cephradine provide abroad-spectrum antibiotic effect when Gram-positive organisms are suspected to be the causative factor of the infection. Cephalosporins are indicated in endodontic practice as they exhibit good bone penetration. Azithromycin has shown enhanced pharmacokinetics in encountering the anaerobes involved in endodontic infection. The oral dosage of azithromycin is 500 mg loading dose followed by 250 mg once a day for five to seven days. Ciprofloxacin is one of the common drugs used for endodontic infections. The effective action against oral anaerobes, Gram-positive aerobic organisms demand the need of ciprofloxacin for endodontic infections. Metronidazole is a synthetic antimicrobial agent, which is bactericidal and most effective against anaerobes. The recommended dosage is 1000 mg loading dose followed by 500 mg every six hours for five to seven days. Clindamycin remains the second drug of choice next to penicillin in treating of odontogenic infections. Due to its adverse side effects, the routine use of clindamycin is not advised.

CONDITIONS WARRANTING PRECAUTIONS FOR THE USE OF ANTIBIOTICS

Antibiotic use may be associated with unfavorable side effects, ranging from gastrointestinal disturbances to fatal anaphylactics shock and development of resistance.

Consideration for antibiotic prophylaxis should begin in patients with kidney and/or liver failure, cardiac patients, pediatric patients, in pregnant or lactating mothers, and immune compromised patients.

1. Renal

Many antibiotics are actively eliminated through kidney. Thus, almost all antibiotics, except cloxacillin, clindamycin, metronidazole and macrolides, required dose modification in patients with renal insufficiency. Dose adjustment can be carried out by reducing the amount administered in each dose or by increasing the interval between doses (without modifying the amount of drug).

2. Hepatic

Some antibiotics are metabolized in liver followed by elimination in bile. Patients with liver failure require a dose reduction of erythromycin, clindamycin, metronidazole and anti-tuberculosis drugs.

3. Pregnant and Lactating Mothers

Almost all antibiotics are contraindicated during pregnancy as a result of their major side effects.

Tetracyclines and aminoglycosides usage leads to teratogenic effects on the fetus (Table 52.7). In general, all antibiotics can cause three potential problems for nursing infants:

1. They can modify the bowel flora and alter gut defense mechanisms; this can result in diarrhea and malabsorption of nutrients.
2. They may have direct effects that may or may not be dose related.
3. Often ignored, is that antibiotics can alter and interfere with microbiological culture, resulting in babies being investigated for sepsis.

4. Cardiac

Infective endocarditis is an uncommon but serious and often life-threatening condition.

Antibiotic prophylaxis not only acts by destroying bacteria, but also by inhibiting bacterial adherence. It is indicated in high-risk dental procedures in patients with pre-existing high-rate cardiac disorders. The standard regimen includes high doses of amoxicillin in children and adults, one hour before the dental treatment, 0.2 g of oral amoxicillin should be given to adults before the dental procedure commencement.

Table 52.7: FDA Risk classes of antibiotics used during pregnancy

Category risk factor	*Antibiotics*	*Side-effects*
A. Satisfactory well-controlled studies on humans showing no hazard to the fetus		
B. Animal studies demonstrate no risk, but no human studies have been performed or human studies have demonstrated risk	Amoxicillin Cephalexin Chlorhexidine Clindamycin Erythromycin Metronidazole Penicillin	
C. Studies on animals establishing fetal hazards and no exact studies on human being	Azithromycin Moxifloxacin Clarithromycin Doxycycline Tetracycline	 Chondrotoxic in growing rats Chondrotoxic in growing rats Increased risk of miscarriage
D. Evidence of risk to the fetus can be used in exceptional cases or circumstances		Intrinsic dental staining Intrinsic dental staining
E. The hazards of using the drug in pregnant women far more than the benefits		

Clindamycin is recommended in patients allergic to beta-lactams. In patients allergic to penicillin or amoxicillin, the first-generation oral cephalosporin is recommended. Vancomycin and streptomycin are used prophylactically for prevention of infective endocarditis in patients with prosthetic heart valves. The negligence to administer antibiotic prophylaxis for dental procedures may result in subacute bacterial endocarditis (SBE) and will lead to worst consequences for the patient.

It is important to note, however, that when antibiotic prophylaxis is called for due to congenital heart concerns, they should only be considered when the patient has:

- Cyanotic congenital heart disease (birth defects with oxygen levels lower than normal), that has not been fully repaired, including children who have had a surgical shunts and conduits.
- A congenital heart defect that been completely repaired with prosthetic material or a device for the first six months after the repair procedure, and.
- Repaired congenital heart disease with residual defects, such as persisting leaks or abnormal flow adjacent to a prosthetic patch or prosthetic device.

Antibiotic prophylaxis is not recommended for any other form of con genital heart disease.

5. Pediatric

Anatomical and physiological differences between children and adults such as the amount of their body water and fat, the maturation of the immune system, the volume of protein, and the level of liver enzymes should be considered while prescribing antibiotics for children. Dentists treat children with antibiotics to reduce the risk of bacteremia caused by dental infections; however, antibiotic therapy should not be used as an alternative for elimination of an infection source.

6. Immunocompromised

Immunocompromised patients represent a special division for dental professionals as they are more prone to bacteremia, which may rapidly lead to septicemia. Invasive dental procedure like dental extraction, deep periodontal scaling should be avoided whenever feasible. The dental procedures performed for the immune compromised patients should be carried after interacting with the hematologic, oncologic and microbiologic consultants. Other indications requiring the need of antibiotic regimen before the commencement of dental procedures include dental implant placement, surgery beyond tooth apex, intraligamentary local anesthetic injections and subgingival placement of antibiotic fibers.

Physician consultation is advised before and after organ transplant. Patients treated with corticosteroids for a long time may require an additional need of corticosteroids to prevent adrenal crisis. The dose is doubled if the patient is on 30–40 mg per day of hydrocortisone for a month. Dental treatment is safer, when performed three months after surgery. Six months is considered the best time and antibiotic prophylaxis is necessary if any invasive dental treatment is to be performed.

Conclusion

Antibiotic therapy is mandatory and essential in medicine and dentistry. Antibiotics are used as adjunctive in addition to adequate debridement and surgical drainage. The guide line recommends against using antibiotics for most pulpal and periapical conditions and instead recommends only the use of dental treatment and, if needed, over-the-counter pain relievers such as acetaminophen and ibuprofen.

As an alternative of prescribing antibiotics, dentists should prioritize dental treatments. If a patient's condition progresses to systemic involvement, showing signs of fever or malaise, then dentists should prescribe antibiotics.

Antibiotic prophylaxis is a necessary option in cases of immunosuppressed patients, patients with a history of cancer, individuals with infective endocarditis, patients with metabolic disorders (such as diabetes and splenectomies), patients with prosthetic joints, indwelling catheters, neurosurgical shunts, valvular heart diseases, surgical pulmonary shunts, hypertrophic cardiomyopathy, mitral valve prolapsed, and prosthetic heart valves. Dentists must weigh the benefits and risks of antibiotics and make an informed decision with their patients on the appropriateness of using antibiotics and may want to consider the following.

- The overall health and immunity of the patient
- Pre-existing conditions of the patient
- The type and location of the infection
- Whether the infection shows signs of spreading
- If the condition can be treated with surgical treatment.
- If the patient has symptoms other than localized pain.

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Chapter
53

Treatment in Medical Emergencies

CARDIAC ARREST

Cardiac arrest is sudden cessation of the heart activity resulting in an inadequate cerebral circulation which leads to coma within one min. If hypoxia is relieved within 3 minutes, the recovery would be complete. If hypoxia exceeds 4–5 min, severe and permanent brain damage occurs.

The airway, breathing and circulation are maintained simultaneously as rapidly as possible as follows. Check for response by arousing the patient, speaking verbally. Check for breathing by feeling air movement around the nostrils and chest rise and activate the emergency response system.

Get the AED (defibrillator) and return to the victim to check a pulse and begin cardiopulmonary resuscitation (CPR).

Follow these steps to locate the carotid artery pulse:

- Locate the trachea, using 2 or 3 fingers.
- Slide these 2 or 3 fingers into the groove between trachea and the muscles at the side of the neck, to feel the carotid pulse. Feel for a pulse for at least 5 seconds but not more than 10 seconds. If you don't feel the pulse, begin CPR, starting with chest compressions.
- Check brachial pulse in case of infant. Place the index and middle fingers gently on the inside of the upper arm for at least 5 seconds but not more than 10 seconds to feel the pulse.

Follow these Steps for CPR (Fig. 53.1)

Position yourself at the victim's side. Make sure the victim is lying faceup on a firm flat surface. Put the heel of one hand on the centre of the victim's chest on the lower half of the breastbone. Put the heel of your other hand on top of the first hand. Straighten your arms and position your shoulders directly over your hands. Press down with each compression (one and half inches for adults), use 2 fingers in the centre of the infants chest just below the nipple line. If there are 2 rescuers, continue chest compressions and Ambu bag air breathing in a ratio of 15:2 in infants and 30:2 in adults. The 2 thumb encircling hands technique is the preferred 2 rescuer chest compression technique. Many infants and children develop respiratory arrest or bradycardia before they develop cardiac arrest. If such children, starting prompt CPR before development of cardiac arrest, they have high survival rate.

Make sure you push straight down on the victim's breastbone. Deliver compressions in a smooth fashion at a rate of 100/min. At the end of each compression, make sure that the

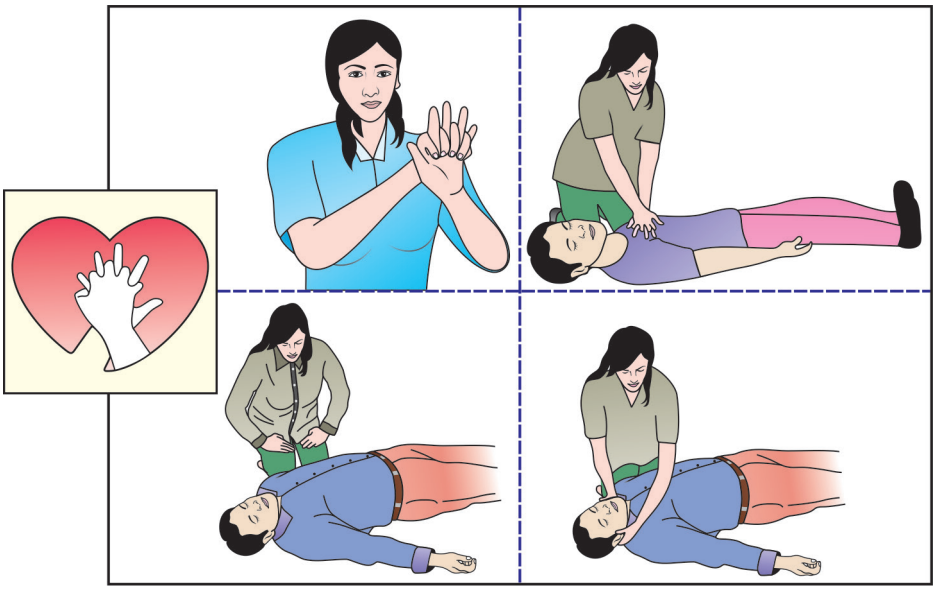

Fig. 53.1: CPR cardiopulmonary resuscitation

chest recoils completely as it allows blood to flow into the heart. The chest compression and chest recoil times should be approximately equal.

Opening the airway for breaths: Place one hand on the victim's forehead and push with your palm to tilt the head back. Place the fingers of the other hand under the bony part of the lower jaw near the chin. Lift the jaw to bring it forward. The head tilt chin lift maneuver lifts the tongue, relieves airway obstruction. For mouth to mask breaths, use a mask with or without 1 way valve. The 1 way valve allows the rescuer's breath to enter the victims mouth and nose and diverts the victim's exhaled air away from the rescuer.

Giving mouth to mask breaths: Position yourself at the victim's side. Place the mask on the victim's face, using the bridge of the nose as a guide for correct position. Seal the mask against the face, place the index finger and thumb along the edge of the mask with the closer hand. Place the remaining fingers of your second hand along the bony margin of the jaw and use the jaw tilt chin lift to open the airway. When you lift the jaw, press firmly and completely around the outside edge of the mask to seal the mask against the face. Deliver air over 1 second to make the victim's chest rise. If the victim has a head or neck injury and you suspect a spine injury, 2 rescuers can use jaw thrust to open the airway. Place one hand on each side of the victim's head, resting your elbows on the surface on which victim is lying. Place your fingers under the angles of the victim's lower jaw with both hands, displacing the jaw forward. If the lips close, push the lower lip with your thumb to open the lips.

Bag and mask ventilation—is used when 2 rescuers are there, one doing CPR and the other bag and mask ventilation and switching roles when tired. Use the thumb and index finger of one hand to make a C on the side of the mask, pressing the edges of the mask to the face. Use the remaining fingers to lift the angles of the jaw to open the airway. Squeeze the bag to give 2 breaths over 1 second after 30 compressions. The patient must be ventilated 10–12 times per minute.

Mouth-to-mouth breathing—is a quick effective way to provide oxygen to the victim. The rescuer's exhaled air contains approximately 17% oxygen and 4% carbon dioxide. This is

enough oxygen to meet the victim's need. Maintain a head tilt chin lift to keep the airway open. Pinch the victim's nose tightly with thumb and forefinger and make a mouth-to-mouth seal. Provide 2 mouth-to-mouth breaths. Make sure, the chest rises with each breath. Give each breath in one second.

1. AEDs are available in different models with a few differences. All AED operate in basically the same way.
2. Attach AEDs pads to the victim's bare chest. Choose adult pads for victims 8 years and older. Peel the backing away from the AED pads. Place one AED pad on the victim's upper right chest and place the other pad to the side of the left nipple, with the top edge of the pad a few cm below the armpit.
3. Clear the victim and analyze the rhythm. The AED may take about 5–16 seconds to analyze. The AED will tell about shockable rhythm.
4. Clear the victim before delivering the shock. Press the shock button. Put jelly on pads before delivering shock to prevent burning of skin. The shock will produce a sudden contraction of the victim's muscles.
5. If no shock is needed and after any shock delivery, immediately resume CPR, starting with chest compressions. After 2 minutes of CPR, the AED will prompt you to repeat steps 3 and 4. The effectiveness of shock delivery decreases significantly for every additional 10 seconds that elapses between last compression and shock delivery.

Stroke: Refers to acute neurological impairment that follows interruption in blood supply to a specific area of the brain. The major types of stroke are ischemic stroke which accounts for 87% of all strokes caused by an occlusion of an artery to a region of the brain. Hemorrhagic stroke accounts for 13% of all strokes and occurs when blood vessel in the brain suddenly ruptures into the surrounding tissue. Fibrinolytic therapy is contraindicated in this type of stroke. Avoid anticoagulants.

The signs and symptoms of a stroke may be subtle. They are:

- Sudden weakness or facial numbness, numbness of arm or leg, especially unilateral.
- Sudden confusion
- Trouble speaking or understanding
- Sudden trouble walking
- Dizziness or loss of control of balance or coordination
- Sudden severe headache with no known etiology.

Cincinnati prehospital stroke scale identifies stroke on the basis of 3 physical findings:

Facial droop: have the patient smile or try to show teeth, one side of the face does not move as well as the other side.

Arm drift: Have the patient close eyes and hold both arms out with palms up, one arm does not move or one arm drifts down compared with the other

Abnormal speech: Patient slurs words, spells wrongly or is unable to speak.

Goals of stroke care:

1. Immediate general assessment by the stroke team should be done within 10 minutes of arrival.
2. Neurological assessment by the stroke team and CT scan within 25 minutes of hospital arrival should be done.

3. **Initiation** of fibrinolytic therapy in appropriate patients within 1 hour of hospital arrival and 3 hours from symptom onset is the golden rule.

Additional stroke care includes support of the airway, oxygenation, ventilation and nutrition. Normal saline is given 75 to 100 ml/hour to maintain intravascular volume. IV or subcutaneous insulin is given to lower blood glucose in patients with acute ischemic stroke when serum glucose is >185 mg/dl.

For fibrinolytic therapy, BP must be less than 185/110 to limit the risk of bleeding complications.

Choking: Due to foreign body airway obstruction in adults and children—ask the victim if he or she is choking. If the victim nods yes and cannot talk, severe airway obstruction is present and you must try to relieve the obstruction.

In a child or adult, the Heimlich maneuver is used. The steps are:

1. Kneel or stand behind the victim. Encircle your hands around the victim's waist from behind. Use one hand to make a fist.
2. Place the thumb side of your fist against the victim's abdomen in the midline, slightly above the navel and well below the breastbone.
3. Grasp your fist with your other hand. Press your fist into the victim's abdomen with quick forceful, upward thrust.
4. Repeat thrusts until the object is expelled from the airway.
5. If the choking victim does not respond, activate the emergency response system. Lower the victim to the ground and begin CPR without checking for pulse.

Clearing an object from an infant's airway requires a combination of back slaps and chest thrusts.

The steps are:

1. Kneel or sit with the infant in your lap.
2. Undress the infant's chest.
3. Hold the infant face down with the head slightly lower than the chest, resting on your forearm.
4. Deliver 5 back slaps, placing the free hand on the infants back, with the palm of one hand supporting the face and jaw.
5. Turn the infant and hold the infant faceup, with your forearm resting on your thigh. Keep the infant's head lower than the trunk.
6. Provide 5 quick downward chest thrusts in middle of the chest over the lower half of the breast bone. Repeat this sequence of backs laps and chest thrusts until the object is removed.

Advanced life support: Once the basic life support is maintained, see the defibrillator for arrythmias or cardiac arrest rhythms. Make IV access–give appropriate drugs to control rhythm and blood pressure. Send arterial blood gas analyses to find the reversible causes like hypovolemia, hypoxia, acidosis, hypo/hyperkalemia, hypothermia, tension pneumothorax, cardiac tamponade, toxins, pulmonary thrombosis, coronary thrombosis, which can be appropriately corrected. If the defibrillator machine shows ventricular tachycardia, ventricular fibrillation, then give shock of 200 J. If the pulse does not return, then give adrenaline 1 mg every 5 minutes followed by shock, then amiodarone 300 mg bolus and second dose 150 mg for refractory VF/VT. The IV fluids can be 1–2 L normal

saline or lactated Ringer. If the rhythm shows asystole/pulseless electrical activity (PEA), no shock is required, give adrenaline 1 mg every 3–5 min. CPR has to be continued for 2 minutes after giving shock and vasopressors. If the breathing is not there as by chest rise, consider endotracheal intubation and wave form capnography to confirm and monitor ET tube placement. There should be 8–10 breaths/min with continuous chest compressions. The main determinant of end tidal CO_2 is blood delivery to the lungs. If $PETCO_2$ abruptly increases to a normal value of 35 to 40 mm Hg, it is reasonable to consider this is an indicator of return of spontaneous circulation (ROSC). If it is <10 mm Hg, it is reasonable to improve chest compressions and vasopressor therapy.

To protect the brain and other organs, induced hypothermia for 12 hours is recommended in adult patients who remain comatose with ROSC after out of hospital VF cardiac arrest. The target temperature of 32 to 34 C for a period of 12 to 24 hours is achieved by rapid infusion of ice-cold, isotonic, non glucose containing fluid, surface cooling devices or icebags. Concurrent PCI and hypothermia are reported to be feasible and safe.

STROKE ADAMS SYNDROME

Stroke adams syndrome is a transient syncope or unconsciousness due to cerebral ischemia because of poor or absent ventricular output. A sharp blow over the precordium may be enough to start it. External pacing should be done till a permanent pacemaker is inserted. The following drugs can be given in case of ventricular asystole

a. Isoprenaline 0.1 to 0. 4 mg injected IV or 1 mg in a drip of 200 ml of 5% glucose.
b. Adrenaline 0.5 ml of 1:1000 IV
c. Sodium bicarbonate 100 ml of 7.5% sol. can be given IV to combat acidosis.
d. Steroids inj hydrocortisone 100 mg IV to relieve edema.

PULMONARY EMBOLISM

Pulmonary embolism is blockade of the pulmonary vasculature by blood clots, venous thrombi, fat, air, foreign bodies or fragments of malignant tumour.

Management

1. **Relief of pain:** The severe pain can be relieved by opiates like inj pethidine 100 mg IM or morphine 15 mg IM.
2. Anticoagulants, usually heparin is given in the dose of 10, 000 to 15,000 units IV followed by 5000–10000 U IV every 6 hours for at least 7 days. Heparin both inactivates already formed thrombin and higher dose inhibits aggregation of platelets.
3. **Thrombolytic or fibrinolytic therapy:** Streptokinase or urokinase 5000–6000 IU are useful to lyse the clot by injecting into pulmonary artery through a catheter. The clot lyses in 3–5 days.
4. **Digitalis:** 0.5 mg is rapidly given IV to increase output of failing right ventricle.
5. **Isoprenaline:** 0.5–1 mg IV and repeated if required. It increases cardiac output and heart rate in case they are low.
6. **Antibiotics:** Ampicillin 500 mg 6 hourly should be given to control the infection in case of pulmonary infarction.

Surgery: Emergency pulmonary embolectomy is the treatment of choice.

Preventive: Pulmonary embolism is precipitated by various factors and prevented by:

1. Prolonged immobilization in bed should be avoided in the elderly.
2. The posture should be frequently changed.
3. Active and passive movements of the lower limbs should be carried out.
4. Dehydration should be prevented and anemia, obesity and infections should be treated.
5. Low dose heparin in critically ill patients—5000 U SC 12 hourly should be given.

HEMOPTYSIS

Hemoptysis is expectoration of blood. There can be two types of hemoptysis:

- **True hemorrhage** from the lungs, the bronchial tree and trachea.
- **Pseudohemorrhage** from the nose, mouth, nostrils and larynx.

Causes of True Hemoptysis

1. **Cardiac cause:** Mitral stenosis, aneurysm of aorta, LVF and primary pulmonary hypertension.
2. **Respiratory disease:** Pneumonia, tuberculosis, bronchogenic carcinoma and adenoma, pulmonary embolism, lung abscess, bronchiectasis, infections of lung and bronchi, trauma to the airways and lung and AV malformations.
3. **Immunological:** Goodpasteur's syndrome, Wegner's granulomatosis and polyarteritis nodosa.
4. **Bleeding disorders:** Thrombocytopenic purpura, agranulocytosis, leukemia, hemophilia and anticoagulant therapy.
5. **Iatrogenic:** Following bronchoscopy, lung biopsy, endotracheal intubation, anticoagulant therapy
6. **Pseudohemoptysis:** Trauma of mouth, pharynx and larynx, tuberculosis, syphilis or pyogenic infection of mouth, pharynx and larynx, malignancy of mouth, pharynx and larynx.

The hemoptysis is bright red and frothy, causes coughing and trickling sensation in throat.

Treatment

Usually, hemoptysis is scanty and stops spontaneously. If it is massive, the following treatment should be given. Diazepam 5–10 mg may be given as tranquiliser. For treatment of shock, blood must be collected for the estimation of Hb, packed cell volume (PCV) and grouping and crossmatching. IV normal saline must be started. Blood transfusion may be required if Hb and PCV are falling. Head low position and intermittent oxygen may be given. Codeine must be given to suppress cough which prevents normal clotting after hemorrhage. The patient should be given bedrest in semi reclining position and leaning on the elbow of the affected side to minimize aspiration. Treatment of the underlying cause and bronchial aspirations is done to prevent atelectasis.

HEPATIC COMA

Hepatic encephalopathy is a reversible disturbance of brain function due to liver disease and due to portosystemic shunting of blood. The precipitating factors are ascites tapping or surgery, pneumonia, GI bleeding and portal vein thrombosis, electrolyte disturbance,

high protein diet and diarrhea. The clinical features of hepatic coma are due to the action of nitrogenous toxins on the brain. Many toxins which fail to get metabolized in the liver reach the brain through blood circulation.

Management: The precipitating factors should be treated or avoided. Oral proteins are to be discontinued because of deleterious effect of ammonia that is formed in the GIT. Parenteral aminoacids can be given as they prevent endogenous nitrogen breakdown. Measures that affect intestinal bacteria are:

Neomycin 4 g/day or ampicillin 2–4 g/day to sterlise the bowel and reduce endogenous ammonia production. Lactoacidophilus bacillus lowers the colonic pH which alters the gut flora and reduces the intestinal absorption of ammonia. Cleaning enema and bowel washes should be done.

Fluids, electrolytes and calories are administered parenterally, 1200 calories are given in form of 10–25% dextrose. Hypokalemia is a common complication and 60 m EQ/day of potassium should be given slow IV in 3 divided doses. Lactic acidosis is treated with parenteral sodium bicarbonate.

Infection should be controlled with antibiotics.

Neurotransmitters—L dopa in hepatic coma as there is defect in the neurotransmitters. L dopa in 1–4 g orally raises the levels of normal intracerebral neurotransmitters. Bromocriptine —2–5–15 mg daily improves encephalopathy as an adjuvant.

Artificial hemoperfusion is to clear the amino acids from the blood in view of severe hyperamino aciduria in fulminant hepatic failure. Mannitol IV 500 ml helps in lowering the raised intracranial tension.

HYPERNATREMIA

Is increase in serum sodium. The treatment depends upon the underlying cause:

1. When water loss is accompanied with no sodium loss, oral replacement with water or IV dextrose is adequate.
2. When water loss is accompanied by loss of electrolytes too, Ringer's lactate solution may be used.
3. If there is increased body sodium, in addition to water replacement, a diuretic like furosemide 40 mg may be given.

HYPONATREMIA

Hyponatremia is diminished serum sodium.

1. **Fluid restriction:** The intake of fluid is restricted below the urinary and insensible fluid losses.
2. When neurological manifestations occur due to hyponatremia, the electrolyte imbalance must be corrected with normal or hypertonic saline 3% IV. The amount of sodium required can be calculated as:

   Sodium deficit = (Normal sodium-patient sodium) 0.6 × Body weight (kg)

   Saline infusions should be avoided in dilutional hyponatremia.

The treatment of cause of hyponatremia should be instituted. In syndrome of inappropriate ADH secretion (SIADH), demeclocycline or Li salts may be given whereas in dilutional hyponatremia, along with water restriction, judicious use of diuretics is useful.

HYPERKALEMIA

Hyperkalemia is rise in serum potassium level.

Management: To counteract the action of potassium and cause its intracellular shift:

1. **Calcium gluconate**—10–30 ml of 10% solution is injected IV slowly. It antagonizes the toxic effects of potassium but does not reduce serum potassium level.
2. **Glucose insulin drip**—500 cc of 5–10% glucose is given in a drip with 20–30 U of insulin. Potassium ions enter the cell along with glucose with the help of insulin.
3. Sodium bicarbonate 100–200 ml of 7.5% cause a change in pH temporarily.
4. **Hemodialysis:** In a case of chronic renal failure, hemodialysis itself can reduce the potassium levels.
5. **To remove potassium from the body:** Cation exchange resin (Kayexalate) is used.
6. The treatment of the primary disease, e.g. Addison's disease with steroids, hypoaldosteronism with 9 alpha-fluorohydrocortisone helps to correct the serum potassium levels.

HYPOKALEMIA

Hypokalemia is reduced serum potassium levels. The treatment consists of replacement therapy with potassium orally 1 g three times a day. Large deficits require IV potassium in 500 ml 5% glucose drip, each drip containing 40 m EQ of potassium and lasting 6–8 hours.

TETANUS

Tetanus is the disease caused by toxin of *Clostridium tetani* and is characterized by muscular rigidity, spasms and autonomic disturbances. The management is done by keeping the patient in dark room with minimal noise. Antitetanus serum (ATS) 10000 units given IV to neutralize circulating toxin. Injection procaine penicillin 8 lac units should be given daily IM for 8–10 days or one dose of benzathine penicillin 2.4 megaunits should be given to kill the clostridial organisms in the wound. The wound should be kept open as the organisms grow rapidly in anaerobic conditions. High doses of diazepam are given up to 300–400 mg daily. If there are repeated laryngeal spasms, tracheostomy is done to bypass the upper airway. In severe cases, intermittent positive pressure ventilation is done after paralyzing the respiratory muscles with Pavlon. Higher antibiotics may be required for secondary bacterial infection.

The prophylaxis is done by giving tetanus toxoid at sixth, seventh and eighth months as a component of triple vaccine. A booster dose is required at 2 years and subsequently every five years.

RABIES

Rabies is a fatal viral disease of the central nervous system following infected dog bite. It can also occur due to bite of other animals like cat, fox, wolf, etc. The patient is kept in isolation in quiet room with high doses of tranquilisers. Diazepam 5–10 mg 6 hourly is given for anxiety. A Ryle's tube should be passed soon to give fluids because as the disease advances, spasms become more painful. Antirabies serum 40 IU immunoglobulins/kg should be infiltrated into and around the wound IM 1 ml on 0, 3, 7, 14, 28 days post-exposure. The prevention is done by immunization of bitten persons by antirabies vaccine even after the bite because

of long incubation period. Animal must also be immunized and strict quarantine of stray animal must be done. Human diploid cell culture rabies vaccine should be given.

SNAKEBITE

There are 400 species of Indian land snakes and 30 species of Indian sea snakes. Of the land snakes, 40 are poisonous and of the sea snakes 29 are poisonous. The common poisonous land snakes are cobra, Russel viper, saw scaled viper, green pit viper, echis and the krait.

The management includes immobilsation of the affected part in a functional position to reduce the rate of spread of the venom.

- Cover the bite loosely with a clean dry bandage.
- Free incisions of the wound through the fang marks and sucking with suction pump.

Polyvalent antivenom should be given IV for its maximal effect within 24 hours of the bite. Mono valent sera are more specific and more potent and should be used if the snake has been identified. Broad spectrum antibiotics are given to check infection of devitalized part especially in viper bites. Tetanus toxoid should be given to prevent tetanus. Analgesics may be required for pain. In hypovolemia, plasma or albumin may be given to expand plasma volume. Red cells lost due to lyses or bleeding may require packed cells or whole blood.

Specific treatment: In cobra bite, Neostigmine 0.5 mg is given IV every ½ hour for six injections and then if symptoms have reduced, every hourly for three injections followed by one injection every 2–3 hours till the signs of paralyses disappear. In viper bite, bleeding occurs due to defibrination syndrome, resulting in consumptive coagulopathy, and hemorrhagic vasculitis. Antisnake venom (ASV) is given as 15000 units followed by 5000 units every six hours till all the hemorrhagic manifestations disappear. Human fibrinogen 300–600 g are given IV within the first 24 hrs of treatment after effective control of clotting.

Treatment of Complications

1. **Shock:** Hypovolemic shock is best treated with 5% albumin. Dopamine and corticosteroids are used if necessary and electrolyte disturbance is corrected.
2. **Acute renal failure:** Oliguria and hematuria are the earliest signs. It is treated by restoration of fluid and electrolyte balance and administration of mannitol 20% or 200 mg of furosemide. If renal shutdown occurs, hemodialysis may be required.
3. **Respiratory failure:** Leads to hypoxia and hypercapnia. This requires ventilation with a respirator and a proper control of blood gases.

MYAESTHENIC CRISIS

Acute weakness of respiratory muscles. It is managed by tracheal intubation and mechanical ventilation. It is severe form of myasthenia gravis which is an autoimmune disorder characterized by development of antibodies to nicotinic receptors at the muscle endplate. It causes weakness of eye muscles, ptosis, diplopia, changes in facial expressions, impaired speech, weakness in arms, hands, legs, neck. Treatment is with neostigmine oral 15 mg 6 hrly. Corticosteroids offer improvement by immunosuppression. IV methyl prednisolone pulse therapy is given withholding anticholinesterases for 2–3 days. Prednisolone 30–60 mg/day used where not responding to anticholinesterases. Azathioprine and Cylosporine are used as immunosuppressants in advanced cases. Plasmapheresis is also an option to remove antibodies to cause dramatic improvement.

ORGANOPHOSPHORUS COMPOUND POISONING

Organophosphates (Dyflos, Ecothiophate, Malathion, Diazinon, Tabun Sarin, Soman) are irreversible anticholinesterases extensively used as agricultural and household insecticides. Poisoning results in local muscarinic effects—irritation of eye, lacrimation, salivation, sweating, copious tracheobronchial secretions, miosis, blurring of vision, bronchospasm, breathlessness, involuntary defecation and urination. The systemic effects are due to muscarinic, nicotinic and central actions—fall in BP, bradycardia/tachycardia, arrhythmias, vascular collapse, muscle fasciculations, respiratory paralysis leading to death. There can be irritability, disorientation, unsteadiness, tremors, ataxia, convulsions, coma and death.

Removal of unabsorbed poison can be done by inducing vomiting, hypertonic saline or gastric lavage. Atropine 2 mg IV repeated every 10 min till dryness of mouth appears to counters the muscarinic effects. Oximes counter the nicotinic effects of organophosphorus poisoning and used early when nicotinic effects like fasciculations or paralysis are present. PAM (Pralidoxime) is the most commonly available oxime in the dose of 1 g IV slowly and repeated after 30 min. Children—20–40 mg/kg.

ATROPINE POISONING

Drug overdose or consumption of seeds and berries of dhatura plant cause Belladona poisoning. Patient presents with dry mouth, difficult swallowing and talking, dry flushed hot skin, urinary retention, decreased bowel sounds, scarlet rash, dilated pupil, photophobia, palpitation, hypotension, weak and rapid pulse, CVS collapse with respiratory depression. Treatment is as follows:

- Gastric lavage is done with tannic acid.
- Patient kept in dark quiet room.
- Physostigmine 1–3 mg SC/IV antagonizes central and peripheral effects.
- Diazepam to control convlusions.
- Maintain airway, breathing, circulation.

CARBON MONOXIDE (CO) POISONING

Carbon monoxide poisoning results from accidental or suicidal inhalation of CO. The toxic effects of CO are due to its high affinity for Hb which is 200 times more than that of oxygen. The patient should be removed from his environment immediately and the patient should be given mouth to mouth respiration 100% O_2 should be given through oronasal pack. Endotracheal intubation should be done if required and the patient may be put on a respirator. Initial hypoxia damages capillary endothelium and causes cerebral edema. Mannitol, furosemide and glycerol should be given. All clothing should be loosened. Fluid and electrolyte balance must be maintained.

DROWNING

Drowning is asphyxiation from submersion in water. If drowning is in fresh water, the aspirated water enters the circulation producing hemodilution, severe hemolysis and hyperkalemia. If it occurs is salt water, the aspirated fluid is hypertonic and thus causes diffusion of the blood into the alveoli resulting in pulmonary edema. Immediately after the patient is rescued, respiratory support should be given by clearing the airway and giving mouth to mouth respiration. If the carotid pulse is not palpable, an external cardiac massage

should be given. The patient should be transferred to the hospital and basic life support continued. Even if respiration and circulation are adequate, the patient must be hospitalized for at least 48 hours for observation. The airway should be cleared and a cuffed endotracheal tube should be passed. In sea water divers, hypovolemia occurs and they should be treated with plasma expanders like dextran. Blood transfusion is done if there is massive hemolysis. Acidosis is corrected by 7.5% sodium bicarbonate. Furosemide 40–80 mg IV is useful in pulmonary edema. Hydrocortisone 100 mg IV 8 hourly is used in very ill patients. A broad-spectrum antibiotic like ampicillin or tetracycline is used to prevent aspiration pneumonitis.

BURNS

Burn is an injury to tissue caused by heat, electricity, chemicals, radiation or cold.

Epidemiology: Definitive data about the number of patients suffering from burn injuries is not available but it is estimated that approximately 1 million patients in India have moderate-to-severe burn injuries every year and in world over, an estimated 1,80,000 deaths are caused by burns every year.

Etiology

a. **Scalds:** Burns caused by steam or hot water, common in children.
b. **Flame burns:** Caused by fire, commonly by housefires (kitchen accidents)
c. **Electric burns:** Can be low voltage <1000 volts or high voltage >1000 volts.
d. **Chemical:** These include acid and alkali burns with alkali burns being more severe especially if eyes are involved.
e. **Radiation burns:** Can be localised or generalized.
f. **Cold:** Can be as a result of Industrial accidents (liquid nitrogen) or frost bite.

The outcome of burn injury depend on respiratory tract injury, percentage of burns and degree of burns.

Respiratory tract injury: These injuries are common when the person in trapped in a confined place like a burning house or vehicle. Inhaled gases can cause respiratory tract burns (supraglottic, subglottic) and certain gases like carbon monoxide can cause metabolic poisoning.

Percentage of burns: This signifies the surface area involved in burns. Rule of Nine is a very simple way of estimating the burn surface area. The body is divided in 11 segments each comprising 9% making a total of 99% and 1% is meant for the genitalia.

Head and neck: 9%
Upper limb: 9% × 2
Front of lower limb: 9% × 2
Back of lower limb: 9% × 2
Upper of half of anterior torso: 9%
Lower half of anterior torso: 9%
Upper half of back: 9%
Lower half of back: 9%
Genitalia: 1%

For small burns, patient's hand is taken as a reference, the hand comprising 1%.
In hospital setting, Lund and Browder chart is an accurate way of messaging area of burns.

Depth of burns: Signified by degree of burn

- **First degree:** Involves the epidermal layer of skin, causes redness, pain and burning sensation, e.g. sunburn.
- **Second degree:** Involves the dermal layer of skin but some part of dermis is always left intact, characterized by blisters, pain.
- **Third degree:** Involves complete skin, whole of dermis is involved, skin becomes hard and leathery. These are painless burns as the nerve endings are destroyed.

Criteria for Admission

1. More than 10 to 15% area involved
2. At extremes of age
3. Hand, feet, face or genitilia are involved
4. Any associated injury
5. History of psychiatric illness
6. Doubts of non-accidental injury
7. Suspected airway burns

Management: The initial management is to check for:

a. Airway
b. Breathing
c. Circulation
   - Any associated injury is to be looked for
   - Fasciotomy is to be considered if a compartment syndrome is suspected especially in patients of electric burns
   - Tetanus prophylaxis is to be done
   - **Pain:** Appropriate analgesics are to be administered

Airway burns: If suspected from history, are to be managed early. An early intubation is indicated in cases of supraglottic burns as once laryngeal edema sets in, intubation becomes difficult. If carbon monoxide poisoning is suspected, oxygen inhalation is indicated.

Fluid management: Intravenous fluids are needed for children with burns more than 10% and in adults with burns more than 15%.

The most widely used formula for fluid resuscitation is the Parkland formula. Ringer's lactate is the fluid commonly used.

The amount is calculated as:

4 ml × weight of the patient in kg × Burn percentage

Half of the calculated volume is given in first 8 hours and the other half in the next 16 hours.

The adequacy of fluid given is monitored by urine output which should be

0.5 to 1 ml/kg body weight/hour

Wound Management

First degree burns: They heal spontaneously within a week, only reassurance and analgesics are required.

Second degree burns: From clinician point of view, these are the most important type of burns, if managed properly by dressings and if infection does not supervene, these wounds heal in 2 to 3 weeks' time, but if the area gets infected, they convert into third degree burns and may require surgical intervention (Fig. 53.2).

Fig. 53.2: Second degree burns (*Image courtesy:* Surgery Burns unit, Jolly grant, Dehradun)

Third degree burns: They are deep burns and if surface area of more than 3 to 4 cm^2 is involved, they require surgical intervention in the form of debridement followed by coverage of raw areas. The debridement is done by technique of tangential excision, (getting rid of dead tissue layer by layer until healthy bleeding is seen). The raw area is then covered with split skin graft or flaps, as indicated (Fig. 53.3).

For topical treatment of burns:

1. Silver sulphadiazine 1%
2. Silver nitrate 0.5%
3. Mafenide acetate.

Complications: Burn is a disease with high morbidity and mortality, the complications responsible for high morbidity and mortality are:

1. **Infections:** Patients with large percentage of burns are immuno-compromised and also because of the exposed tissue, the chances of infection are very high. Appropriate antibiotics according to culture and sensitivity reports, following stringent measures of sterilization, early debridement are the key measures to avoid and treat infections.
2. **Gastrointestinal ulcers:** These occur as a result of mucosal ischemia and are called curling ulcers they are managed by prophylactic antacids.
3. **Hypertrophic scars:** This is a common problem after burn wound healing especially when deep wounds are allowed to heal by conservative management. Early excision and grafting of burn wounds avoids these problems.
4. **Contractures:** Patients with deep burns involving joints if treated conservatively end up with contractures, these patients require contracture release and coverage.

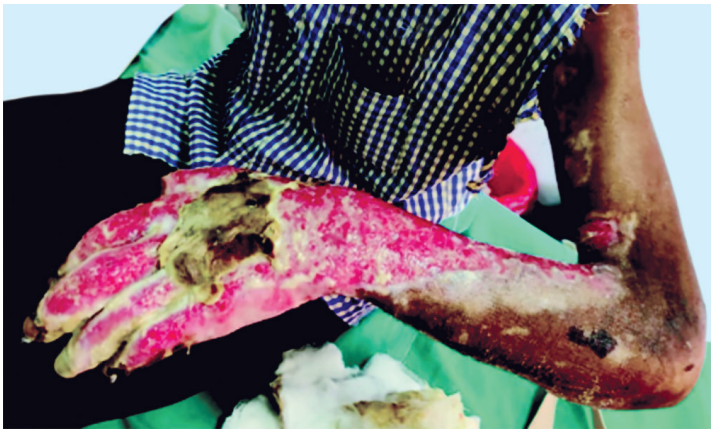

Fig. 53.3: Third degree burns (*Image courtesy:* Surgery Burns unit, HIMS, Jolly Grant, Dehradun)

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Chapter
54

Dengue and Management

Dengue is viral infection transmitted by mosquito bite caused by *Aedes aegypti* which is common in tropical and subtropical areas of the world.

- **Pathophysiology:** The typical incubation period for the disease is 4 to 7 days. The first targets are skin macrophages and dendritic cells. The infected cells then move to the lymph nodes moving through the lymphatic system to other organs. Before the onset of symptoms, viremia may be present for 24 to 48 hours. The host and viral factors complex interaction determines the severity of infection whether it will be asymptomatic, typical, or severe. Severe dengue fever is characterized by increased microvascular permeability and shock syndrome. Expanded dengue syndrome refers to unusual or atypical manifestations in patients with dengue with neurological, hepatic, renal, and other isolated organ involvement. Common laboratory findings include thrombocytopenia, leukopenia, elevated aspartate aminotransferase.
- Rapid laboratory identification of dengue fever from1st day onwards includes NS1 antigen detection. Serologic tests are only useful after several days of infection and may be associated with false positives due to other flavivirus infections, such as yellow fever or Zika virus. The virus antigen is detectable by ELISA, polymerase chain reaction, or virus isolation from body fluids. Serology will reveal a marked increase in immunoglobulins. IgM capture enzyme-linked immunosorbent assay (MAC-ELISA) is used.
  - **Management of dengue fever (DF)**—is based on treatment of symptoms. Supportive management is planned (Fig. 54.1).
  - Antipyretics are used to normalize the body temperature.
  - Consensus guidelines for treatment of dengue fever from the World Health Organization and US Centers for Disease Control recommend acetaminophen to manage pain and fever but contraindicate non-steroidal anti-inflammatory agents (NSAIDs) due to increased bleeding risk, with thrombocytopenia as a complication.
- Oral intake of fluids and electrolytes is advised for patients with excessive dehydration like sweating, vomiting or hypotension.
- In DHF endemic areas, monitoring of patients for 24–48 hours should be done until they become afebrile and after hematocrit levels are stable, platelet count is >50,000/mm^3 or improving.

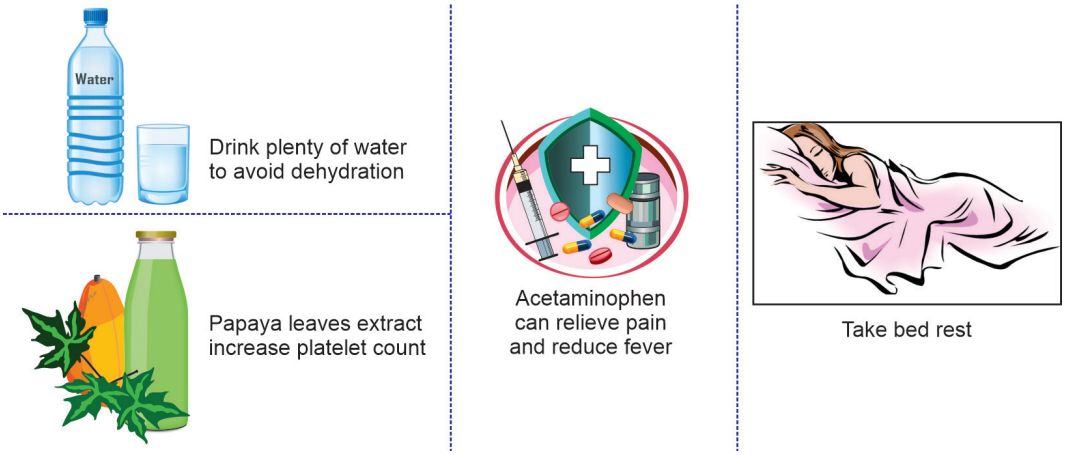
Water
Drink plenty of water to avoid dehydration
Papaya leaves extract increase platelet count
Acetaminophen can relieve pain and reduce fever
Take bed rest

Fig. 54.1: Treatment of dengue fever

MANAGEMENT OF FEBRILE PHASE

- Tepid sponging of forehead.

  Drugs:

  – *Children:* Paracetamol 10 mg/kg PO every 6 h.

  – *Adults:* Paracetamol 500 mg PO every 6 h.
- Encourage the intake of oral fluids. Oral rehydration solution (ORS) and/or fruit juices are preferred over plain water.
- If the patient cannot drink, drinks little, or is dehydrated, initiate IV fluids (based on the Holliday–Segar formula), with lactated Ringer's solution or 0.9% NSS (2–4 ml/kg/h).
- The initial signs of shock should be closely looked for. Fluid balance should be maintained (Fig. 54.2). Oral administration should be resumed as soon as possible.
- The febrile phase transits to the afebrile stage usually after the third day of illness and is critical period.
- Serial hematocrit determinations and Hb are deciding factors for treatment, since they assess the degree of plasma leakage and need for IV fluids administration.
- Hematocrit determination should be done daily from the third day until the temperature has normalized for 1–2 days.

Dengue Hemorrhagic Fever (DHF)

- **Management of (DHF) Grade I and II (Fig. 54.3):** Person who has dengue fever with low platelet count and hemo-concentration and presents with nausea, vomiting, pain in abdomen, black tarry stools, epistaxis, bleeding from the gums, wet purpura on buccal mucosa, etc. needs hospitalization and signs of shock should be looked for.
- The shock stage develops generally during transition from febrile to afebrile phase of illness.
- A rise in hematocrit indicates IV fluid infusion.

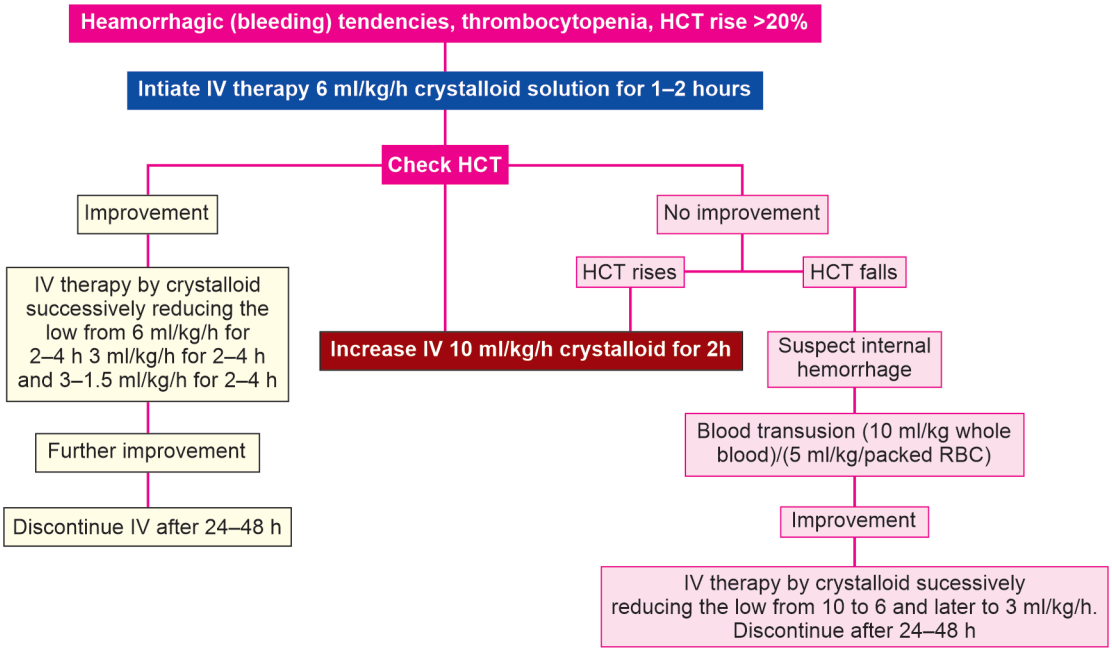
Heamorrhagic (bleeding) tendencies, thrombocytopenia, HCT rise >20%
Intiate IV therapy 6 ml/kg/h crystalloid solution for 1–2 hours
Check HCT
Improvement
No improvement
HCT rises
HCT falls
IV therapy by crystalloid successively reducing the low from 6 ml/kg/h for 2–4 h 3 ml/kg/h for 2–4 h and 3–1.5 ml/kg/h for 2–4 h
Increase IV 10 ml/kg/h crystalloid for 2h
Suspect internal hemorrhage
Blood transusion (10 ml/kg whole blood)/(5 ml/kg/packed RBC)
Further improvement
Discontinue IV after 24–48 h
Improvement
IV therapy by crystalloid sucessively reducing the low from 10 to 6 and later to 3 ml/kg/h. Discontinue after 24–48 h

Fig. 54.2: Volume replacement algorithm for patients with DHF Grades I and II.

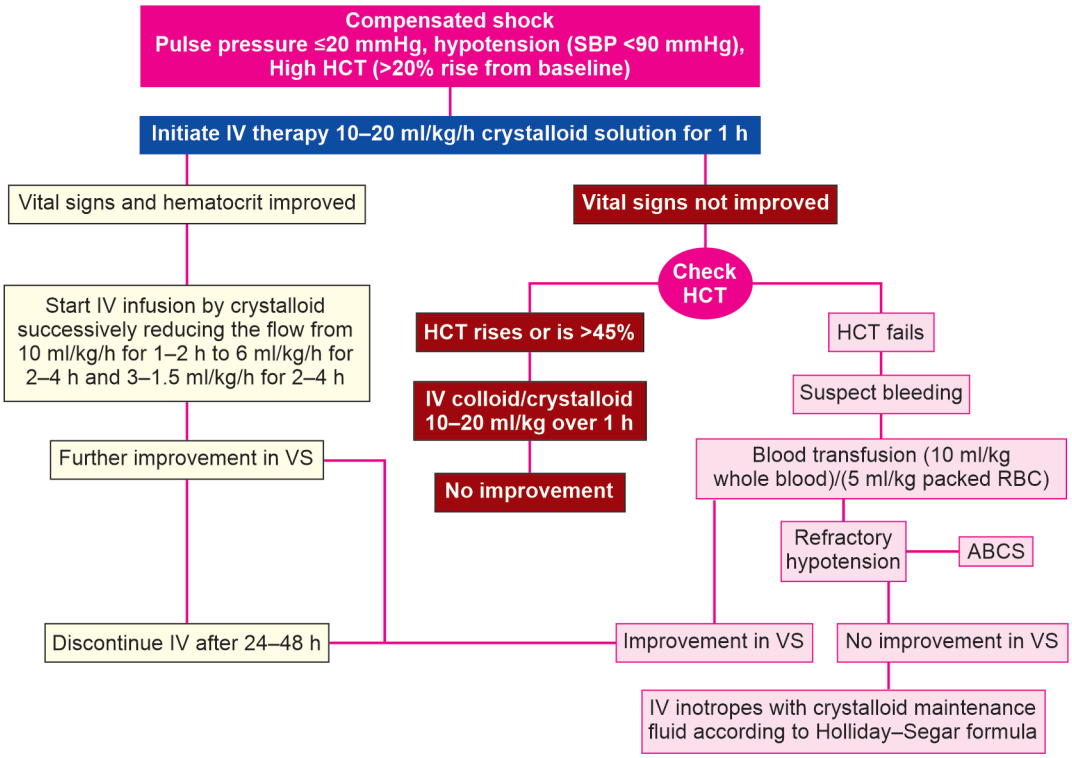
Compensated shock
Pulse pressure ≤20 mmHg, hypotension (SBP <90 mmHg), High HCT (>20% rise from baseline)
Initiate IV therapy 10–20 ml/kg/h crystalloid solution for 1 h
Vital signs and hematocrit improved
Vital signs not improved
Check HCT
Start IV infusion by crystalloid successively reducing the flow from 10 ml/kg/h for 1–2 h to 6 ml/kg/h for 2–4 h and 3–1.5 ml/kg/h for 2–4 h
HCT rises or is >45%
HCT fails
IV colloid/crystalloid 10–20 ml/kg over 1 h
Suspect bleeding
Further improvement in VS
No improvement
Blood transfusion (10 ml/kg whole blood)/(5 ml/kg packed RBC)
Refractory hypotension
ABCS
Discontinue IV after 24–48 h
Improvement in VS
No improvement in VS
IV inotropes with crystalloid maintenance fluid according to Holliday–Segar formula

Fig. 54.3: Treatment of compensated shock

DHF Grade III/IV-Shock (Fig. 54.4)

Dengue hemorrhagic fever occurs primarily in children <10 years living in endemic areas and requires prior infection with the dengue virus. Dengue hemorrhagic fever often begins with abrupt fever and headache. Warning signs that predict possible progression to severe dengue include severe abdominal pain and tenderness, persistent vomiting, hematemesis, epistaxis or bleeding from the gums, black, tarry stools (melena), edema, lethargy, confusion, or restlessness, hepatomegaly, pleural effusion, or ascites, marked change in temperature (from fever to hypothermia), circulatory collapse and multiorgan failure, called dengue shock syndrome, may develop rapidly 2 to 6 days after onset.

Bleeding tendencies: Manifest as usually as purpura, petechiae, or ecchymoses at injection sites, sometimes as hematemesis, melena, or epistaxis, occasionally as subarachnoid hemorrhage.

Bronchopneumonia with or without bilateral pleural effusions is common. Myocarditis can occur. Hemorrhagic manifestations include at least a positive tourniquet test and petechiae, purpura, ecchymoses, bleeding gums, hematemesis, or melena. Mortality is usually <1% in experienced centers but otherwise can range up to 30%.

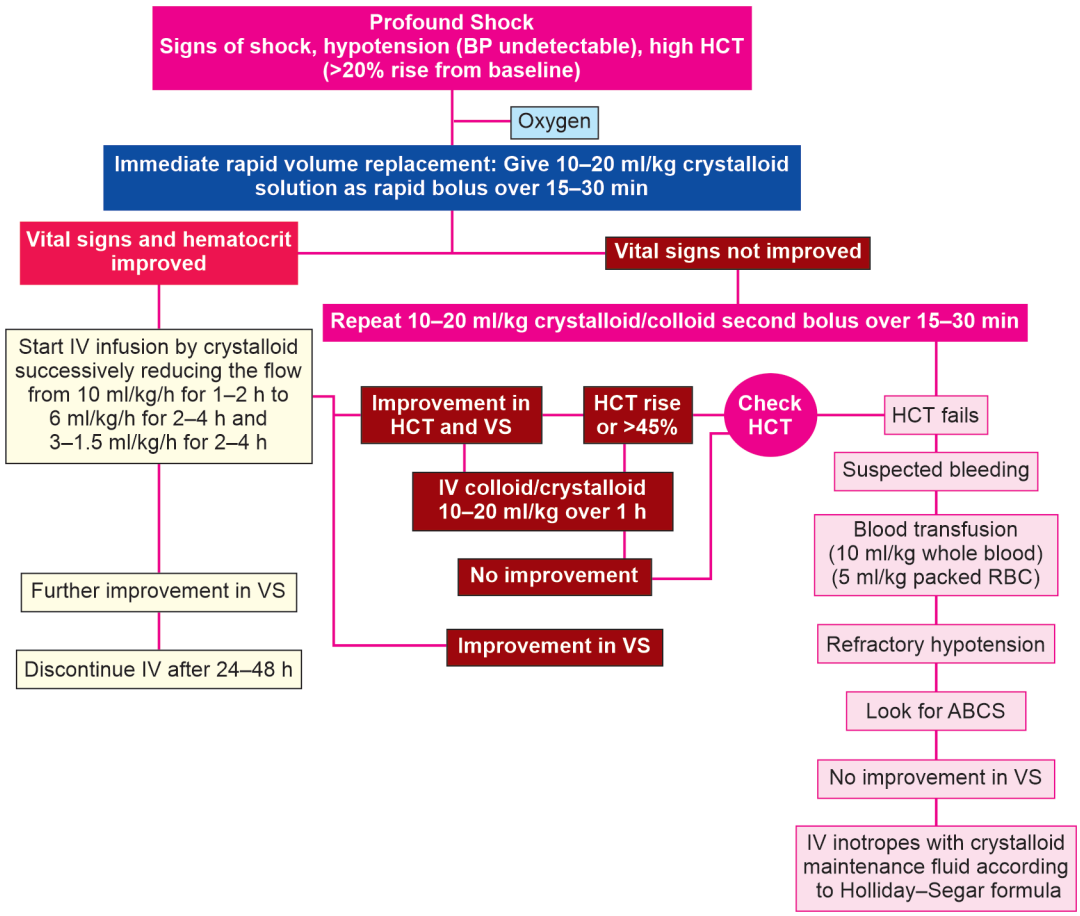
Profound Shock
Signs of shock, hypotension (BP undetectable), high HCT (>20% rise from baseline)
Oxygen
Immediate rapid volume replacement: Give 10–20 ml/kg crystalloid solution as rapid bolus over 15–30 min
Vital signs and hematocrit improved
Vital signs not improved
Repeat 10–20 ml/kg crystalloid/colloid second bolus over 15–30 min
Start IV infusion by crystalloid successively reducing the flow from 10 ml/kg/h for 1–2 h to 6 ml/kg/h for 2–4 h and 3–1.5 ml/kg/h for 2–4 h
Improvement in HCT and VS
HCT rise or >45%
Check HCT
HCT fails
Suspected bleeding
Blood transfusion (10 ml/kg whole blood) (5 ml/kg packed RBC)
IV colloid/crystalloid 10–20 ml/kg over 1 h
No improvement
Refractory hypotension
Look for ABCS
No improvement in VS
IV inotropes with crystalloid maintenance fluid according to Holliday–Segar formula
Further improvement in VS
Discontinue IV after 24–48 h
Improvement in VS

Fig. 54.4: Treatment of profound shock

Complete blood count, coagulation tests, urinalysis, liver tests, and dengue serologic tests should be done. Coagulation abnormalities include thrombocytopenia [100,000 platelets/μl (100×10^9/L)], a prolonged prothrombin time (PT), prolonged-activated partial thromboplastin time (PTT), decreased fibrinogen, increased amount of fibrin split products.

Management: The mainstay of therapy for DSS is the rapid restoration of circulating plasma volume. The management guidelines by WHO, first proposed in 1975, recommended initial volume replacement with crystalloid solutions—1000 ml, followed by colloids–albumin/starch for patients with refractory shock.

Fluid therapy: The required fluid volume is calculated on the basis of body weight and charted on 1–3 hourly basis or even more frequently in the case of shock. The severity of dengue fever decides the regimen of the flow of fluid and the time of infusion. Fluids should be given in 24 hours period for adequate intravascular volume maintenance and circulation.

- **Dengue without shock syndrome:** 1 L normal saline, then 150 ml/hour, O_2 therapy. Hb and hematocrit change from baseline every 6 hours. Maintenance fluid 100 ml/hour. For IV fluid administration of patients with DHF, four regimens of fluid are given in escalating doses: 3 ml/kg/hour; 6 ml/kg/hour; 10 ml/kg/hour and 20 ml/kg/hour.
- **Indications of blood transfusion:** In case of hematocrit falling still, fresh whole blood transfusion 10–20 ml/kg/dose should be given. (Persistent shock state in spite of resuscitation with fluids and plasma expanders indicate internal bleeding and actual assessment of the amount of bleed is not possible). In case of severe bleeding, patient should be hospitalized and investigations are done to look for the cause and site of bleeding and immediately bleeding should be stopped.
- Internal bleeding like gastrointestinal (GI) bleeding may be sometime severe and difficult to locate.
- Patients of severe bleeding may have deranged liver function tests.
- However, alternative treatment is with proper IV fluid or plasma expander (i.e. haemaccel) in absence of blood.
- **Indications of platelet transfusion (Fig. 54.5):** Platelet transfusion is done in case thrombocytopenia with active bleeding. Prophylactic platelet transfusion may be given at level of <10,000/mm^3 in absence of bleeding manifestations.

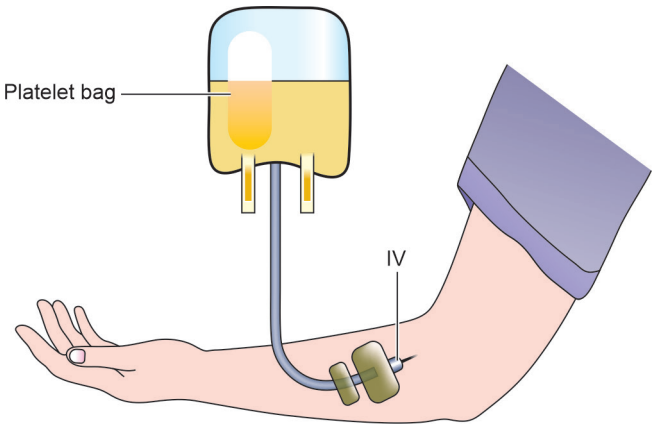

Fig. 54.5: Platelet transfusion

- Platelet transfusion may also be given in prolonged shock with coagulopathy and abnormal coagulogram.
- In case of systemic massive bleeding, platelet transfusion may be needed in addition to red cell transfusion.
- With very low platelet count, fundus examination is done to rule out retinal hemorrhage. Rarely, intracranial bleed may also occur in some patients, who have severe thrombocytopenia and abnormal coagulation prole.
- Oxygen should be given to all patients in shock.

DOSE OF PLATELET TRANSFUSION

- Standard dose for adults is 5–6 units of random donor platelets, or 1 unit of apheresis platelets or 1 unit of buffered coated pooled platelets (BCPP) equivalent to 3×10^{11} platelets.
- Single donor platelets are more potent than random donor platelets. 1 SDPC is equivalent to 6–8 units of RDPC. SDPC are prepared by the platelet apheresis procedure in which a portion of the donor's platelet and some plasma is removed and RBCs, WBCs and remaining plasma are returned back to donor.
- RD PC are prepared from donated blood within 4–6 hours of collection by centrifugation and it contains 5.5×10^{10} platelets.
- Use of fresh frozen plasma/cryoprecipitate in coagulopathy with bleeding should be as per the advice of physician and patient's condition.

Criteria for admission of a patient: DF patient should be admitted in hospital if he/she has significant bleeding from any site, signs of hypotension, persistent high-grade fever, rapid fall of platelet count, sudden drop in temperature.

- Dengue patients with warning signs and symptoms—should be admitted and closely monitored.
- Dengue infection having comorbidities are considered to be moderate dengue even though there is no evidence of capillary leakage or bleeding.

Criteria for discharge of patients: Patients with normal BP, adequate urine output, no respiratory distress, persistent platelet count >50,000/mm^3 should be discharged from hospital.

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Chapter
55

Treatment of COVID SARS-2

Corona virus infectious disease caused by corona virus belonging to COVID SARS2 family, first made its appearance in 2019, Wuhan province of China.

DIAGNOSIS OF COVID-19

When to suspect:

- All symptomatic individuals contacting acute respiratory infection, who have travelled abroad in the last 14 days.
- All healthcare professionals who are symptomatic with symptoms of ARI (fever and cough) or shortness of breath.

Asymptomatic direct and high-risk contacts of a confirmed case, (i.e. those who live in the same household with a confirmed case and a healthcare professional who examined a confirmed case) should be tested once between day 5 and 14) after contact.

Investigations: Rapid antigen test, RTPCR test.

Adults with COVID-19 can be categorized into following groups:

1. **Asymptomatic or presymptomatic infection**—individuals who test positive for SARS COV-2 by virological testing using a molecular diagnostic (e.g. PCR) or antigen test. But have no symptoms.
2. **Mild illness:** Persons with any of the various signs and symptoms of COVID-19 like fever, cough, sore throat, malaise, headache.
3. **Moderate illness:** Individuals with presence of clinical features of dyspnoea or hypoxia, fever, cough, RR 24/min, and O_2 saturation 94 on room air at sea level.
4. **Severe illness:** Individuals with clinical signs of pneumonia + any of the following–RR >30/min, severe respiratory distress, SpO_2 90 on room air.
5. Critical illness may be associated with ARDS, septic shock.

Treatment

Category A: Asymptomatic/mild symptoms.

- Investigations CBC/RBS, LFT/KFT/CX-ray PA view, ECG.
- Tab PCM 650 mg SOS.
- Vitamin C 500 mg BD/betadine gargle/steam inhalation.
- Tab ivermectin 12 mg stat.

- Tab hydroxychloroquine (HCQ) 400 mg BD on day 1 then 200 mg BD for 4 days.
- Tab azithromycin 500 mg OD × 5 days.
- Tab oseltamivir 75 mg BD × 5 days.

Group B—symptomatic, 3 out of 4 symptoms—fever >100 F, dry cough, myalgia, shortness of breath.

- **Investigations:** Liver function tests (LFT), kidney function tests (KFT), amylase, ferritin, LDH, CK, PT-INR, Mg, C X-ray PA view, ECG.
- **Treatment:** Tab PCM 650 mg SOS.
- Tab vitamin C 500 mg BD.
- Zinc supplementation/steam inhalation.
- Tab ivermectin 12 mg stat.
- Tab azithromycin 500 mg OD × 5 days.
- Tab oseltamivir 150 mg BD × 5 days.
- **Antibiotic as per clinical condition:** Ceftriaxone/ceftazidime.
- Lopinavir/ritonavir 200 mg/50 mg 2 TAB BD × 5 days.
- Judicious use of IV steroids (methylprednisolone 1–2 mg/kg/day for 5 out of 7 days.
- ECG if patients age is >40 or history of heart disease and if QTc is prolonged.

Group C—severe pneumonia, supplemental O_2 therapy is immediately administered to patients with severe acute respiratory infection (ARI) and respiratory distress, hypoxemia.

- Initiate O_2 therapy at 5 lts/min and titrate flow rates to reach SPO_2 90.
- In children to target SPO_2 94.
- Serum ferritin is high, C reactive protein (CRP) is high.
- Acute respiratory distress syndrome (ARDS) (Acute onset): New or worsening respiratory symptoms within 1 week of clinical insult.

Investigations and Treatment

- Chest imaging (X-ray, CT scan or lung US), bilateral opacities, respiratory failure, ECHO to exclude hydrostatic cause of edema.
- Oxygenation in ARDS
- SpO_2/FiO_2 <315 suggests ARDS.
- Use bilevel non-invasive ventilation (NIV) or continuous positive airway pressure (cPAP) >5 cm via full face mask.
- Facemask with reservoir bag at 10–12 L/min gives 80–100% O_2. High flow nasal O_2 (HFNO) at 15 L/min can achieve 80–100%.
- SEPSIS—signs of organ dysfunction include:
  - Altered mental status
  - Difficult fast breathing
  - Life threatening organ dysfunction
  - Low O_2 saturation
  - Decreased urine output
  - Fast HR, weak pulse, cold extremities, skin mottling
  - Lab evidence of coagulopathy, thrombocytopenia, high lactate or hyperbilirubinemia

Hypoxemic respiratory failure in ARDS commonly results from intrapulmonary ventilation perfusion mismatch or shunt. Prone position for 12–16 hours improves oxygenation. NIV

is not advised in patients with unstable hemodynamics, multiorgan failure and abnormal mental status.

Management of septic shock: Septic shock in adults is diagnosed when (lactate <2 mmol/litre), mean arterial pressure (MAP) <60) despite good hydration. Vasopressors are needed to maintain mean arterial pressure 65 mm Hg. Within 1 hour of diagnosis, antimicrobial therapy and fluid loading is started. Fluids 30 ml/kg crystalloids in 1st 3 hours are infused.

Drugs for COVID-19

COVID-19 is caused by novel CORONA virus SARS COV-2. It is spread by inhalational route. It causes spectrum of diseases ranging from asymptomatic to severe critical characterized by rapidly developing respiratory failure.

Treatment remains largely symptomatic and depends upon the stage of severity. Mild cases require symptomatic treatment for fever, cough or cold.

SOS administration of tab paracetamol (10 mg/kg) for fever is recommended. In non-responding cases, mefenamic acid can be added.

For cough, cough suppressant preparations can be used. Antihistaminic (cetrizine or fexofenadine) can be used in usual doses for a few days. In refractory cough, inhaled budesonide (800 µg twice daily) can be taken.

No role of OTC prescription of antibiotics (azithromycin or doxycyline) could be established in mild cases.

If symptoms persist for more than 5 days, tests must be performed to know progression of disease.

Antivirals, anti-inflammatory therapy and immune based therapy can be used.

In moderate to severe cases, treatment is largely supportive. Oxygen inhalation, assisted ventilation, prophylactic or therapeutic anticoagulation with heparin or LMWH are recommended.

Antivirals

Remdesivir: The FDA has approved an antiviral drug called remdesivir to treat COVID-19 in adults and children who are age 12 and older. **Remdesivir** is a newly developed antiviral drug, inhibits viral RNA polymerase. Its useful in COVID-19 if used early in moderate-to-severe disease. Remdesivir may be prescribed for people who are hospitalized with COVID-19 and need supplemental oxygen or have a higher risk of serious illness. Its usual dose is 200 mg IV infusion once on day 1 followed by 100 mg for 4 days. Usual side effects are nausea, and elevation of liver enzyme. Safety in pregnancy is not proven.

Molnupiravir: Molnupiravir is an antiviral medication that inhibits the replication of certain RNA viruses. Molnupiravir is a prodrug of the synthetic nucleoside derivative N4-hydroxycytidine and exerts its antiviral action through introduction of copying errors during viral RNA replication. The FDA has authorized for emergency use of it to treat mild-to- moderate COVID-19 in adults who are at higher risk of serious illness and not able to take other treatments. The emergency use authorization was only narrowly approved as efficacy is doubtful and molnupiravir's mutagenic effects could create new variants that evade immunity and prolong the COVID-19 pandemic. Use in pregnancy is not recommended.

Breastfeeding is not recommended during treatment due to potential adverse reactions in the infant. Use in patients under 18 years of age can affect bone and cartilage growth. Usual doses are 800 mg daily for 5 days. In India, its available in 200 mg cap.

Favipiravir—is a broad spectrum oral antiviral drug, inhibits RNA-dependent RNA polymerase. It is found to be useful in COVID-19 if used early in mild-to-moderate disease. Its usual dose is 1800 mg twice daily on day 1, followed by 800 mg twice daily up to 14 days. Usual side effects are nausea, anemia, elevation of liver enzyme and renal failure. This drug is contraindicated in pregnant and lactating mothers.

Paxlovid—the FDA has authorized for emergency use a drug called paxlovid. This drug combines two types of medications in one package. The first drug is nirmatrelvir, which blocks the activity of a specific enzyme needed for the virus to replicate. The second drug is an antiviral drug ritonavir, which helps slow the breakdown of nirmatrelvir. Paxlovid is authorized to treat mild to moderate COVID-19 in people age 12 and older who are at higher risk of serious illness. The medications are taken orally.

Baricitanib: The FDA has authorized for emergency use the rheumatoid arthritis drug baricitinib to treat severe or critical COVID-19 in some cases. The drug is a JAK inhibitor having dual action of mechanism. It promotes the cellular immunity by increasing the lymphocytes mechanism and inhibits the dysregulated humoral immune mechanism by inhibiting the IL-6 formation and the succeeding cascades of reaction. It is also said to have an antiviral action. Baricitinib may be used in hospitalized patients with COVID-19 who need mechanical ventilators or need supplemental oxygen. WHO recommends its use with corticosteroids. Baricitinib is an oral drug, used in the treatment of rheumatoid arthritis. It is not recommended for use in children less than 2 years. The dose is 4 mg once daily for 14 days. Age related dose adjustment and renal dose adjustment is needed.

Anti-inflammatory therapy: Many anti-inflammatory drugs have been studied to treat or prevent dysfunction of several organs and lung injury from infection-associated inflammation.

Dexamethasone: This corticosteroid has anti-inflammatory action that is used to treat or prevent organ dysfunction and lung injury from inflammation. Researches have shown that this drug reduces the risk of death by about 30% for people on ventilators and by about 20% for people who need supplemental oxygen. The US National Institutes of Health has recommended dexamethasone for people hospitalized with COVID-19 who are on mechanical ventilators or need supplemental oxygen. Other corticosteroids, such as prednisone, methylprednisolone or hydrocortisone, may also be used. These corticosteroids may be harmful if given for less severe COVID-19 infection. In some cases, the drugs remdesivir, tocilizumab or baricitinib may be given with dexametha sone as add on drug in hospitalized people who are on mechanical ventilators or need supplemental oxygen.

Tocilizmab: US FDA issued an emergency use authorization for tocilizumab for the treatment of COVID-19 in hospitalized people aged two years of age and older who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), in June 2021. Cytokine storm stage of COVID-19 is associated with abnormally high IL-6 levels. Tocilizumab binds soluble as well as membrane bound interleukin-6 receptors, hindering IL-6 from exerting its pro-inflammatory effects. The usual dose is 6–8 mg/kg, 200–400 mg slow IV infusion as a single dose. It can be repeated if needed.

Th most common adverse effects reported from clinical studies were upper respiratory tract infections, nasopharyngitis, headache, and high blood pressure. The enzyme alanine transaminase was also elevated in at least 5% of patients, but in most cases without symptoms. Among the less common side effects were dizziness, various infections, as well as reactions of the skin and mucosae like mild rashes, gastritis and mouth ulcer. Rare but severe reactions were gastrointestinal perforations and anaphylaxis.

Immune-based therapy: Studies have been done by researchers on immune-based therapies, including convalescent plasma, mesenchymal stem cells and monoclonal antibodies. The FDA has authorized for emergency use **convalescent plasma** therapy to treat COVID-19. Convalescent plasma is blood donated by people after recovery from COVID-19. Convalescent plasma with high antibodies may be used to treat some hospitalized people with COVID-19 who are either early in their illness or have weakened immune systems.

Monoclonal antibody: Monoclonal antibody medications include sotrovimab; a combination of bamlanivimab and etesevimab; and a combination of casirivimab and imdevimab. These drugs are used to treat mild-to-moderate COVID-19 in patients at a higher risk of developing serious illness due to COVID-19. This includes patients who are older, immunocompromised, having comorbidities like diabetes, hypertension, and obesity, and those unvaccinated. Studies are ongoing on the effectiveness of monoclonal antibodies against Omicron but early laboratory studies show that sotrovimab retains its activity. Treatment involves a single infusion given intravenously in an outpatient setting. To be most effective, these medications need to be given soon after COVID-19 symptoms start and before hospitalization. Some monoclonal antibodies are less effective against certain COVID-19 variants. The FDA has also authorized for emergency use the monoclonal antibody combination of tixagevimab and cilgavimab (evusheld) to prevent COVID-19 in some people with weakened immune systems or a history of severe reactions to a COVID-19 vaccine.

Ivermectin: The drug ivermectin is an anti-helminthic drug. The FDA has not approved use of this drug to treat or prevent COVID-19.

Hydroxychloroquine and chloroquine: These malaria drugs were authorized for emergency use by the FDA during the COVID-19 pandemic. However, the FDA withdrew their authorization when data analysis showed that the drugs are not effective for treating COVID-19. They can also cause serious heart problems.

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Textbook of
Clinical Pharmacology

As per the latest NMC Guidelines | Competency Based Medical Education (CBME) Curriculum under Graduate Medical Education Regulation

is a comprehensive text written in a lucid way, covering all fields of medicine to imbibe learning of clinical pharmacology by the undergraduate and postgraduate medical students, interns and residents who aspire to be budding clinicians. It will also serve as a handy reference and quick guide for busy clinicians in practice.

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- Illustrative figures and tables for good understanding and grasping the essentials clearly.
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- Guidelines for treatment of hypertension, diabetes mellitus, asthma, AIDS, dengue are clearly stated.
- Clinical photographs of patients taken in real hospital practice are included to explain diseases pertaining to ophthalmology, dentistry, pediatrics and dermatology.

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